A study of postprostatectomy incontinence: Definitions, clinical measurements, and outcome of surgical treatment

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Acknowledgements

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Abbreviations

AE	Adverse effect
AUS	Artificial urinary sphincter
AMS	American Medical Systems
BCR	Biochemical recurrence
BRFS	Biochemical recurrence-free survival
CI	Confidence interval
DO	Detrusor overactivity
EAU	European Association of Urology
ED	Erectile dysfunction
EPIC-26	Expanded Prostate Cancer Index 26 item Questionnaire
EPIC-50	Expanded Prostate Cancer Index 50 item Questionnaire
ES	Effect size
HADS	Hospital Anxiety and Depression Scale
ISD	Intrinsic sphincter deficiency
NUCG	Norwegian Urologic Cancer Group
OUH	Oslo University Hospital
PCa	Prostate cancer
PPI	Postprostatectomy incontinence
PSA	Prostate specific antigen
PSM	Positive surgical margin
QOL	Quality of life
RT	Radiation therapy
RARP	Robot assisted laparoscopic radical prostatectomy
RP	Radical prostatectomy
RRP	Retropubic radical prostatectomy
RTS	Retrourethral transobturator sling
SF-12	Short Form-12 QOL Questionnaire
TNM	Tumor, Node, Metastasis classification for staging of PCa
UCLA-PCI	University of California Los Angeles Prostate Cancer Index
UID	Urinary Incontinence Domain of the EPIC-26 Questionnaire

List of original papers

This thesis is based on the following papers, which are referred to in the text by the Roman numerals I-III:

Paper I

How should continence and incontinence after radical prostatectomy be evaluated? A prospective study of patient-ratings and changes over time

Holm HV, Fosså SD, Hedlund H, Schultz A, Dahl AA.

J Urol. 2014 Oct;192(4):1155-61. doi:10.1016/j.juro.2014.03.113. Epub 2014 Apr 12.

Paper II

Severe postprostatectomy incontinence: Is there a significant association between preoperative urodynamic findings and outcome of incontinence surgery?

Holm HV, Fosså SD, Hedlund H, Schultz A, Dahl AA.

Scand J Urology 2014. 2014 Nov 27:1-10. doi:10.3109/21681805.2014.980845. Epub ahead of print.

Paper III

Study of generic quality of life in patients operated on for post-prostatectomy incontinence

Holm HV, Fosså SD, Hedlund H, Dahl AA.

Int J Urol 2013 Sep;20(9):889-95. doi:10.1111/iju.12077. Epub 2013 Feb 19.

1. BACKGROUND

1.1. Introduction and summary of the background

General issues

This thesis concerns several aspects of urinary incontinence after radical prostatectomy (RP) for prostate cancer (PCa), such as identification of prevalence and predictors of urinary leakage, results of urodynamic examinations, and outcomes of surgical treatment for persistent urinary leakage.

Currently an increasing number of Norwegian men are diagnosed with PCa every year, close to 5,000 new cases in Norway in 2012 [1]. For patients with clinically localized PCa, RP and radiation therapy (RT) are offered as curative treatment options, with similar oncologic outcomes. Each treatment modality is followed by a typical pattern of adverse effects (AEs). Following RP, erectile dysfunction and urinary leakage are the most frequent AEs. Following RT, urinary irritation, sexual and bowel dysfunctions are common [2]. There is a wide disparity in the reported prevalence rates of these AEs, probably due to different definitions, evaluation methods, and patient samples [3,4].

Before treatment the responsible doctor counsels patients as to eventual oncologic and functional outcomes. The counselling is given on an individual basis according to treatment modality considered and preoperative risk factors present. A crucial aspect of realistic preoperative counselling is that relevant information is available. Hence local and national studies of treatment outcomes are of considerable importance. Based on such outcomes, counselling and rational choices of treatment can be made by the patients. Thereby long-term satisfaction may be achieved within the perspective of having been optimally treated for PCa, accepting the risk of unavoidable AEs.

Postprostatectomy incontinence (PPI)

Reported PPI rates range from 2% to 74%, depending on the definition applied. Potential risk factors for PPI include higher age, preoperative incontinence, comorbidity, and PCa characteristics (clinical stage, clinical PCa risk group, etc.), as well as peroperative technical factors (nerve sparing, apical dissection, bladder neck preservation, surgeon's experience) [3].

Wide anatomic dissection around the prostate during RP can damage the nerve and blood supply of the bladder, bladder neck, sphincter, and urethra, with resulting insufficiency of the continence mechanism and possibly damage to the bladder muscle [5].

PPI can be due to urethral sphincter dysfunction, causing stress incontinence, or bladder dysfunction, causing urgency incontinence, or both (mixed incontinence). The pathophysiology of PPI can be characterized by urodynamic studies, and treatment options for PPI can be selected accordingly. However, surgical treatment of sphincter dysfunction is often required in men with persistent severe PPI, regardless if bladder dysfunction coexists or not. It is not known whether urodynamic bladder dysfunction compromise outcome of surgery for PPI.

For three decades Norwegian patients with persistent severe PPI have been offered surgical treatment at the Department of Urology, OUH Rikshospitalet. Since 2012, a few other hospitals in Norway also offer such surgery, as the demand for surgical treatment of PPI had increased enormously during the previous decade, due to the increased number of RP's as well as increased awareness of the possibility to treat PPI.

Aims of this thesis

On this background this clinical thesis explores different aspects of PPI in three studies:

1) How different methods of evaluating PPI result in different prevalence rates in a prospective study of 844 patients self-reporting AEs following RP (Paper I) [6].

2) The associations between preoperative urodynamic findings and outcome of incontinence surgery in patients with severe PPI (Paper II) [7].

3) Generic QOL and risk factors for poor QOL in patients after surgery for PPI (Paper III) [8].

1.2. Aspects of prostate cancer

1.2.1. Anatomy of the prostate gland and surrounding structures

The prostate gland is primarily an exocrine organ secreting a slightly alkaline fluid that usually constitutes about 30% of the volume of ejaculated semen. Its endocrine function consists of converting serum testosterone to the more potent androgen dihydrotestosterone by the enzyme 5α-reductase. By convention, the prostate is anatomically divided into transition, central, peripheral, and anterior zones, and PCa is usually found in the peripheral zone of the gland.

A thin capsule surrounds the prostate, except from at the apex and base, and a multilayered periprostatic fascia is located externally to the capsule. The pubovesical and puboprostatic ligaments attach the ventral part of the bladder neck, the urethral sphincter and the underlying prostate to the posterior surface of the pubic bone, and these ligaments may be important for urinary continence [9].

The internal and external urinary sphincter and the puborectalis complex of the levator ani muscle all contribute to the urinary continence mechanism. The *pudendal nerve* is somatic and supplies nerve fibres via its intrapelvic branch to the striated muscle fibres in the external urinary sphincter (the rhabdosphincter) and the levator ani muscle. The preprostatic internal sphincter is a continuation of the smooth detrusor muscle and is under alpha-adrenergic control with innervation provided by the *inferior hypogastric plexus* [10].

The urethral rhabdosphincter is a cylindrical structure surrounding the urethra and extending vertically from the perineal membrane to the base of the bladder [11,12]. Its muscle fibres insert cranially into the apex and anterior face of the prostate gland to merge with fibres of the detrusor muscle and caudally into the perineal fascia. This suggests that the action of the rhabdosphincter is to draw the sphincteric complex upward beneath the pubic bone. The anterior and lateral walls of the rhabdosphincter are thick and rich with striated muscle fibres. The posterior wall contains little or no muscle but consists mainly of fibrous connective tissue [11,12]. These aspects are important also in understanding the pathophysiology of incontinence following RP (vide infra).

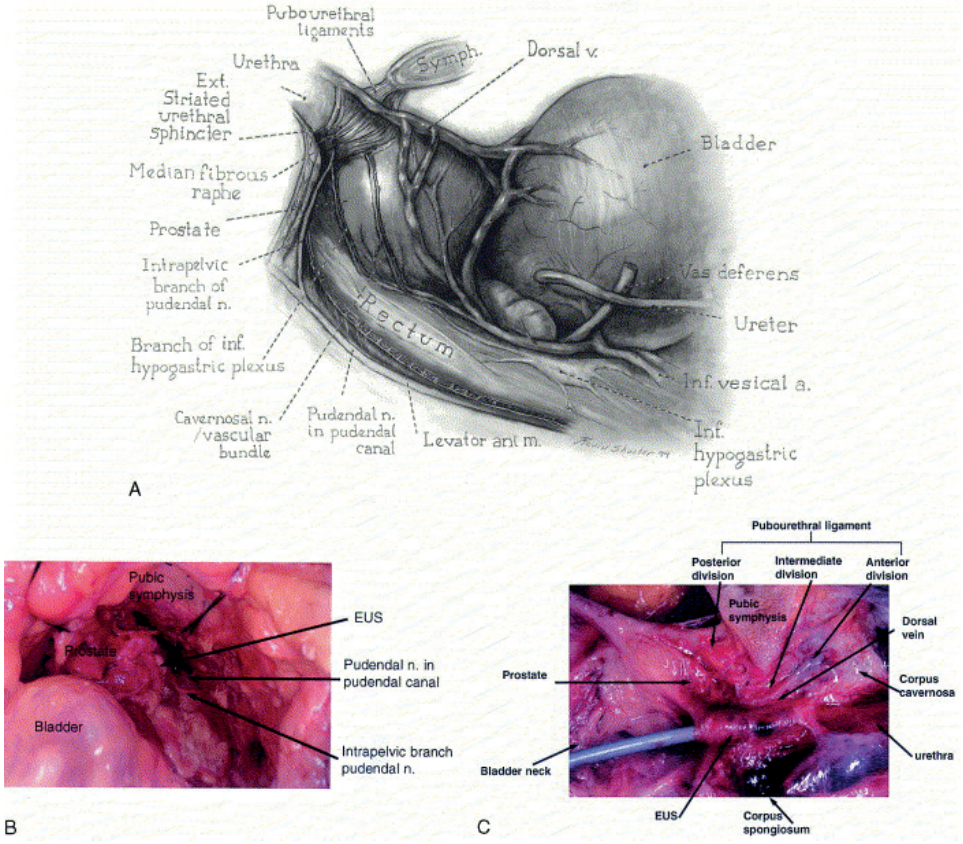

Figure 1. Anatomy of the external striated urethral sphincter (rhabdosphincter)

(A) Sagittal view of the prostate and bladder in the pelvis. B) A surgeon's view of the retropubic space. (C) Sagittal view of the sphincter complex in a fresh-frozen cadaveric specimen [11]. Copyright has been obtained.

1.2.2 Prostate cancer epidemiology and risk factors

Worldwide PCa is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% of the total new cancer cases and 6% of the total cancer deaths in males in 2008 [13]. In *Europe*, PCa is the most common cancer in males accounting for 23% of the total new cancer cases, and 10% of all cancer deaths in 2012 [14]. The corresponding proportions for the *United States* are 27% and 10%, and for *Norway* 29% and 17%, respectively [1].

PCa incidence rates vary widely, which is likely due to differences both in the true underlying prevalence and the intensity of diagnostic efforts. Incidence rates rose rapidly in the early 1990s in countries with higher use of PSA-testing, soon after its introduction.

In Norway, the incidence of PCa has increased four-fold over the last 60 years and there were 4,919 new cases in 2012. Of these, 83% had clinically localized or regional (locally advanced, vide infra) disease and were potential candidates for curative treatment [15]. Approximately one in eight Norwegian men will be diagnosed with PCa before the age of 75 years, most commonly after the age of 50. The mortality rate has been relatively stable with a slight decrease the last two decades, lately around 1,000 deaths annually.

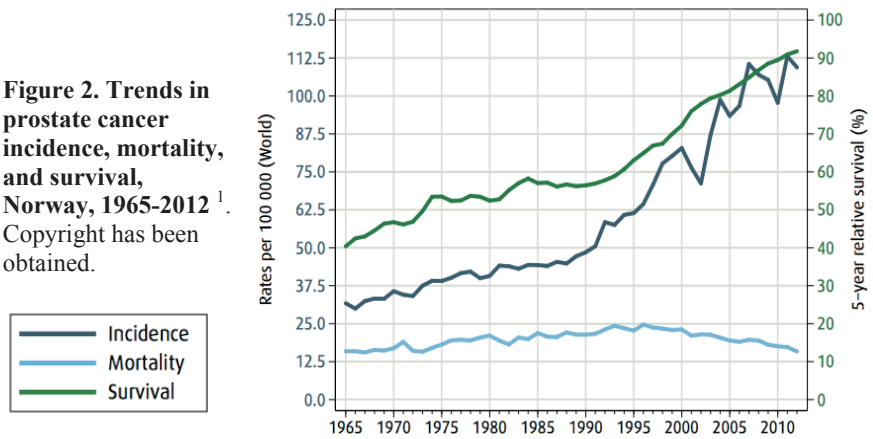

Figure 2. Trends in prostate cancer incidence, mortality, and survival, Norway, 1965-2012 [1]. Copyright has been obtained.

The five-year relative survival rate has increased to 98% for men diagnosed with localized PCa, and 92% for all PCa patients in Norway. The 10-year and 15-year relative survival rates for all PCa patients are 81% and 73%, respectively [15]. Accordingly most men die with PCa rather than of PCa.

Mortality rates may be better estimates of risk and public health significance of PCa than incidence rates. High-resource countries usually have a high incidence as well as a slightly decreasing mortality (Figure 2), suggesting an effect of earlier detection and/or earlier and more effective treatment. However, the increasing incidence and decreasing mortality can also partly be due to 'overdiagnosis'/'overdetection' [16] which occurs when slow-growing cancers are detected, but do not become symptomatic before the patients die of other causes.

Before the introduction of PSA testing, the incidence-mortality ratio was 2:1. This ratio has increased in Western Europe and the USA to 8:1, with a lifetime risk of death due to PCa of about 3%, which illustrates the level of overdiagnosis/overdetection of PCa that will not cause any harm to the patients' health [14,17]. Autopsy studies have revealed PCa in 31-83% of men above 70 years who die from other causes [18].

The risk factors of developing clinically significant PCa are not well known, although three well-established risk factors have been identified: increasing age, ethnicity, and heredity [19].

Chemoprevention of PCa by medications, dietary nutrients, and supplements, has been extensively studied in large prospective randomized trials, however without any results that represent basis for any preventive recommendation [20]. Lifestyle factors, such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation, and occupational exposure, might be involved in the development of PCa, but there is no evidence to justify recommending lifestyle changes in order to reduce the risk of PCa [21].

1.2.3. Prostate Specific Antigen (PSA)

PSA is a protein secreted from the prostate. The PSA level increases in diseases like benign prostate hyperplasia and prostatitis, but also in PCa. PSA testing is therefore used in early diagnostics of PCa, although it has low specificity for clinically significant PCa.

Several modifications of the serum PSA value have been described, which may improve the specificity of PSA in the early detection of PCa. These include PSA density, PSA density of the transition zone, age-specific reference ranges, PSA molecular forms, and the Prostate Health Index (PHI) [22]. PSA velocity (rate of rise of PSA level [ng/ml/year]) and PSA doubling time have limited use in the diagnosis of PCa as prospective studies have not shown superiority over PSA alone [23-25].

The widespread use of PSA testing has resulted in a considerable PCa stage migration; more men present earlier with lower stages, lower grades, and lower PSA at diagnosis of PCa, and fewer men present with incurable metastatic disease. Together with improvements in treatment, this has led to significant decrease in PCa mortality in some countries, but also overdiagnosis and overtreatment [26].

With PSA testing and/or screening of healthy men follows an inherent risk of overdiagnosis, which is the term used when a condition is diagnosed that would otherwise not go on to cause symptoms or death. Overdiagnosis of PCa can be a burden for both the individual patient due to AEs and for society due to healthcare costs, when the cancer is non-progressive or slow growing, as many of screen-detected PCa's are. In fact, PSA-detected cancers might represent overdiagnosis in over 60% [16].

Screening is defined as "The use of simple tests across a healthy population in order to identify individuals who will develop a disease but do not yet have any symptoms" (WHO) [27]. PSA screening for early PCa detection in asymptomatic men, of any age, without family history of PCa, is not recommended in Norway, and there is currently no evidence for introducing widespread population-based screening programs in *all men* in any population [19,28]. However, from 2002 to 2011, PSA testing rates increased, despite several international guidelines that suggest a judicious use of the test [29]. In Norway, an elevated PSA, as opposed to symptoms or clinical findings (DRE), was the reason for further investigation and diagnosing of PCa in 55% of patients in 2012, an increase from around 35% in 2004-2008 [30].

1.2.4. Classification of prostate cancer

Staging

The main tools for diagnosing PCa have traditionally been digital rectal examination (DRE), serum concentration of PSA, and transrectal ultrasound (TRUS). The need for biopsies is determined on the basis of the PSA level, a suspicious DRE finding, the patient's biologic age, any comorbidities, and the therapeutic consequences.

Clinical tumour, node, metastasis (cTNM) staging is a measure of the anatomical extent of the PCa at diagnosis (Table 1) [31]. T describes the extent of the primary tumour, N describes any metastasis to regional lymph nodes, and M describes any distant metastasis. The cTNM stage is one of the most important factors regarding treatment choice and prognosis.

However, the clinical T category (cT), based on DRE, biopsy, and imaging, is associated with a high inter-observer variability causing somewhat uncertain classification. According to the current European Association of Urology (EAU) guidelines, the imaging technique used for local staging should rather be magnetic resonance imaging (MRI) than TRUS since MRI improves the detection and characterisation of PCa compared with TRUS [19,32].

Definite statement as to pelvic lymph node status requires lymphadenectomy with histopathological examination of the resected tissue. MRI or bone scintigraphy can be used to assess metastases in the skeleton, while MRI or computed tomography (CT) can detect metastases in soft tissue.

The EAU guidelines define all non-metastatic PCa as *localized*, which is also done in this thesis. PCa with clinical T category 3-4 is usually specified as *locally advanced* since the PCa of this extension is no longer confined to the prostate [19]. However, in the Cancer Registry of Norway, localized (cT1-cT2) and regional (i.e. locally advanced, cT3-cT4) PCa are registered as separate entities [15].

Table 1. The 7th edition of clinical prostate cancer staging [31]	
T – Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy, but not palpable or visible by imaging
T2	Tumor confined within the prostate
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles [1]
N – Regional lymph nodes [2]	
NX	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M – Distant metastases [3]	
MX	Distant metastasis not assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

[1] External sphincter, rectum, bladder, levator muscles, and/or pelvic wall
[2] Regional lymph nodes (extended lymph node dissection): obturator, external iliac, and hypogastric (presacral)
[3] When more than one site of metastasis is present, the most advanced category should be used

Grading

The Gleason score (1966), named after the American pathologist Donald Gleason (1920-2008), is recommended for histopathological *grading* of PCa and has proved to be important as prognostic factor [19,33,34]. Gleason graded PCa on a scale from 1 to 5 (Figure 3). According to current international convention, the Gleason score of a prostate biopsy consists of the Gleason grade of the most extensive carcinoma plus the highest grade, regardless of its extent, as opposed to the original scoring system that added the most common and second most common pattern [19,35].

The ability to distinguish aggressive from indolent PCa is of great importance to refine PCa detection, decision-making, and care. Epstein et al. identified histological criteria in prostate biopsy specimens that discriminate *indolent* from *clinically significant PCa* [36]. The histological criteria that define *indolent PCa* on biopsy include absence of Gleason grade 4 or 5, PCa limited to three or fewer biopsy cores, and <50% tumor involvement in any individual core [37]. These criteria have been used for inclusion to active surveillance, with the aim of deferring active treatment when not necessary (vide infra).

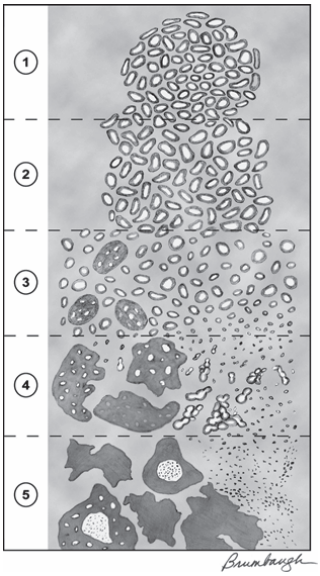

Figure 3.
Gleason grades 1 to 5 [38]
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Risk stratification

PCa risk groups are useful in treatment decision-making and reporting of outcomes. The PCa risk groups are based on pre-treatment PSA, clinical T-category, and Gleason score of prostate biopsies in patients with localized PCa (i.e. non-metastasized) [39]. However, as described above, the role of the clinical T category in these criteria remains controversial.

There are several ways to define risk groups of localized PCa, with some minor differences (Table 2). *The D'Amico risk groups* have been widely adopted [40], and they have been shown to predict PCa-specific survival in patients undergoing curative treatment of PCa [41,42].

- Low-risk PCa according to D'Amico is defined as cT1-2a (tumor involving one-half of one lobe or less) and PSA ≤10 ng/ml and Gleason score <7.
- Intermediate-risk PCa is defined as cT2b (tumor involving more than one-half of one lobe, but not both lobes) *or* Gleason score 7 *or* PSA >10-20 ng/ml.
- High-risk PCa is defined as cT2-T3a (tumor involving both lobes, with or without extracapsular extension, but not the seminal vesicles) *or* PSA >20 ng/ml *or* Gleason score >7 [43].

The current EAU guidelines have slightly different cut-offs than those originally described by D'Amico (Table 2) [19].

Table 2. Defined risk groups of localized prostate cancer [39]

	Very low-risk	Low-risk	Intermediate-risk	High-risk
D'Amico [40,43]		PSA ≤10 [(a)] and GS <7 [(b)] and cT1-2a [(c)]	PSA >10-20, or GS 7, or cT2b	PSA >20, or GS >7, or cT2c-3a
EAU [19]		PSA <10, and GS <7, and cT1c	PSA 10-20, or GS 7, or cT2b-2c	PSA >20, or GS 8-10, or ≥ cT3a
NCCN [(d)] [39]	cT1c GS < 7 PSA < 10 PSAD < 0.15 [(e)] <3 pos. biopsies	PSA <10, and GS <7, and cT1-2a	PSA 10-20, or GS 7, or cT2b-2c	PSA >20, or GS >7, or cT3a

[a]PSA: Prostate Specific Antigen (ng/mL) [b]GS: Gleason score. [c] cT: clinical T stage. [d] NCCN: National Comprehensive Cancer Network. [e]PSAD: Prostate Specific Antigen Density (a quotient of PSA and prostate volume).

1.2.5. Treatment of clinically localized prostate cancer

Overview

The natural history of low-risk PCa is such that the vast majority of affected men will die from other causes than PCa, even without curative treatment of the PCa [42]. However, it is well-documented that the long-term survival is considerably diminished in men diagnosed with intermediate or high-risk PCa [42,44,44].

The established curative treatment options for localized PCa are radical prostatectomy (RP) and radiation therapy (RT) with comparable oncologic outcomes and long-term survival, although randomised studies have not been performed. However, active surveillance (AS), watchful waiting (WW), or non-curative hormone-treatment are also available options for some patients with clinically localized PCa. High-intensity focused ultrasound (HIFU) and cryotherapy have emerged as new alternatives for treating localized PCa, but there is not enough data available to give treatment recommendations [45,46].

Of all men diagnosed with PCa in Norway in 2012, 6% were assigned to AS, 35% underwent RP, and 24% received RT [30]. The proportion that underwent local tumor destruction (predominantly HIFU in Norway) was not reported. In Norway the PCa patient is not always evaluated in a multi-disciplinary team in the diagnostic period, but often evaluated and counselled by the urologist alone, which could to some extent explain the higher use of RP than RT.

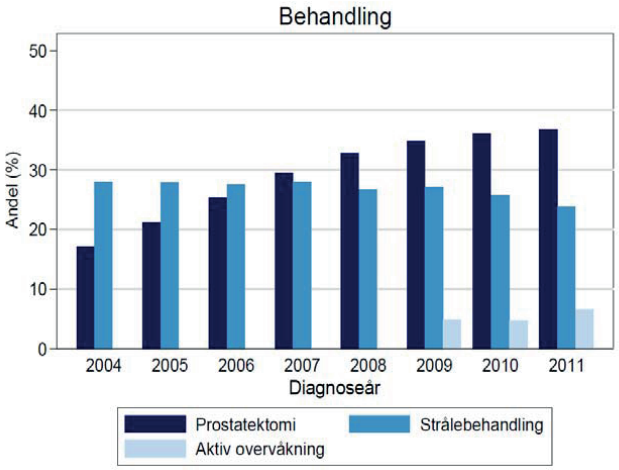

Figure 4. Proportion of PCa patients undergoing RP ('prostatektomi'), RT ('strålebehandling') and AS ('aktiv overvåking') in Norway [30] Copyright has been obtained.

The treatment decision may have long-term implications as each treatment modality is associated with a distinctive pattern of adverse effects (AEs) [2]. While erectile dysfunction and urinary incontinence are more common after RP, urinary irritative symptoms and bowel dysfunction are more common after RT. Therefore, treatment choices should be determined with care in a dialogue between the doctor and the patient, having in mind that curatively intended treatment is not always indicated.

Active surveillance and watchful waiting

Active surveillance (AS) is an option for patients with low-risk PCa and good performance status. Studies on AS in clinically organ-confined PCa have shown a low rate of progression and PCa-specific death in well-selected patients with low-risk disease. The aim is to reduce overtreatment in patients with clinically confined low-risk PCa, holding the option of curative treatment in reserve. The idea was originally based on data demonstrating that men with well-differentiated (i.e. low grade) PCa have a 20-year PCa-specific survival rate of 80-90% [47,48]. AS might mean no treatment at all for patients above 70 years or patients with a life expectancy of less than 10 years, while AS in younger patients might mean a possible treatment delayed for years.

According to Norwegian guidelines, patients with low-risk PCa should be recommended AS after MRI has been performed [45]. Criteria are low-risk PCa (D'Amico) with two or less positive biopsies of at least 8 biopsies, and less than 50% cancer of normal biopsy length. In Norway, AS has not yet become widely accepted as a valid strategy for these men, however. The proportion of patients with low-risk PCa included in AS increased from almost 20% to over 30% in the period 2009-2012, with a similar trend in the United States [49], while the corresponding proportion in Sweden is 65% [30]. At different hospitals in Norway, this proportion varied from less than 30% to 95% [50]. Although the proportion is slowly increasing, there has been a challenge communicating that this is a safe alternative for selected patients.

In patients with PCa not eligible for curative treatment due to old age or comorbidity, watchful waiting (WW) can be a suitable approach of conservative management. WW means that patients remain without treatment until symptoms occur, and will at that time be offered palliative treatment (hormone treatment, transurethral resection of the prostate and/or RT).

Radical prostatectomy

For men with clinically localized PCa that is clinically significant, i.e. intermediate-risk and high-risk PCa, and who have a life expectancy of at least 10 years, surgery is one of the relevant options for curative treatment. The goal of RP is eradication of the PCa by complete removal of the prostate gland and the seminal vesicles with tumour-free surgical margins and preservation of urinary continence and erectile function. The so-called "trifecta outcome" implies that the patient ideally is cancer free, continent and potent after RP. An extended concept, the "pentafecta", includes the trifecta as well as negative surgical margins and no surgical complications [51].

Potential benefits of RP include more than 10 to 15 year disease-free survival when the PCa is localized, better determination of prognosis with pathological staging, and good outcomes with postoperative RT in the adjuvant or salvage setting.

Prior to the 1980's, the surgical anatomy of the prostate and surrounding tissue was poorly understood and the complication rates were high due to intraoperative bleeding and high incidence of postoperative incontinence, erectile dysfunction, and stricture formation [52]. After the description of the anatomy of the dorsal vein complex [53] and the pelvic plexus innervating the corpora cavernosa [54], as well as further description of the pelvic anatomy [55], the operative technique of RP was refined within the following two decades. This led to better preservation of urinary continence and erectile function, and hence substantially increased the use of surgery as treatment for localized PCa (Figure 5) [52,56].

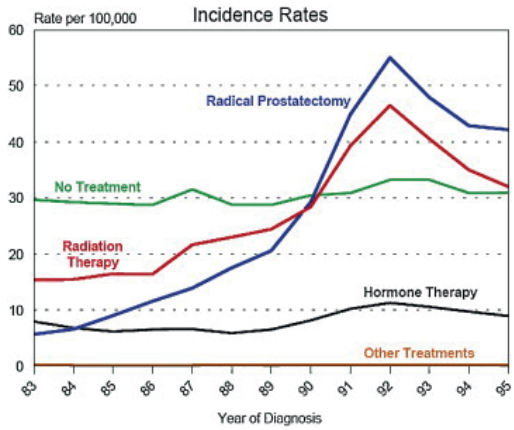

Figure 5. Change of incidence of PCa treatment modalities over time (USA) [56]. Copyright has been obtained.

Perineal RP was first described by the German surgeon Theodor Billroth in 1867 and *retropubic RP* (RRP) was introduced by the British surgeon Terence Millin in 1947 [57,58]. With the incorporation of laparoscopy in urologic surgery, surgeons in Europe were the first to describe the technique and early outcomes with *laparoscopic radical prostatectomy* (LRP) [59]. However, LRP is technically demanding with a long learning curve. As an alternative the *robot-assisted radical prostatectomy* (RARP) was developed at Henry Ford Hospital; Detroit, MI, in 2000 [60]. The telepresence technology was first meant to be used in the military, but was commercialized by the American company Intuitive Surgical into the system called the daVinci surgical system [61]. The big advantage over laparoscopy was better movement of the instruments, that have an extra 'joint' intracorporally, which is of essential value when suturing in the pelvis. Nevertheless, the learning curve for RARP is not as short as previously thought, and a large number of cases is needed to get positive surgical margin (PSM) rates and operative time to a minimum [62].

During the last decade there has been a tremendous growth in adoption of the robot-assisted procedure despite limited data on outcomes and greater costs compared with open RRP. In spite of that, RARP is the first robot-assisted surgical procedure to achieve widespread use, and has become the primary approach for the surgical management of localized PCa in the United States [63,64]. With limited follow-up time and lack of randomized controlled trials, available data suggest that there are similar complications rates, oncologic outcomes, and AEs (incontinence and erectile dysfunction rates) following RARP, RRP and LRP [65-67].

In Norway, the first daVinci surgical system was established at the Department of Urology, OUH Radiumhospitalet, in December 2004 as the second in Scandinavia, and since 2005 no open RP have been done at that department. RARP is currently available at eight hospitals in Norway.

Nerve-sparing RP should be attempted in all men with normal or near-normal preoperative erectile function and organ-confined disease, whether by RRP or RARP, while unilateral nerve sparing procedure is an option in stage T2a-T3a disease [19,68].

The need for and the extent of *pelvic lymphadenectomy* are controversial. The risk of lymph node metastases is low in men with low-risk PCa and <50% positive biopsy cores [69,70]. Surgery for high-risk prostate cancer should aim at achieving either oncological radicality or local debulking, both of which include an extended pelvic lymph node dissection, not only for

staging purposes, but also with a possible therapeutic intent [71]. Norwegian guidelines recommend bilateral extended lymphadenectomy in patients with high-risk PCa and if surgical lymph node (N) staging is indicated [45].

There are diverse opinions regarding the optimal treatment of men with high-risk, clinically localized PCa and management should be discussed in an interdisciplinary team, due to the high risk of positive surgical margins (33-66%) and regional lymph node metastasis (8-49%). Of patients primarily treated with surgery 56-78% eventually require adjuvant or salvage RT or hormonal therapy [19]. On the contrary, about 40% of the patients with high-risk PCa undergoing RP have specimen-confined disease (pT2–pT3a, pN0, and negative surgical margins), and they have excellent long-term outcome [72]. There is also an increasing trend towards using surgical therapy to address locally advanced PCa (cT3) with simultaneous extended lymphadenectomy in selected cases [45,73,74].

Follow-up

In Norway, following RP, the first postoperative visit with the operating surgeon is normally scheduled within six weeks after RP when serum PSA is measured and the oncological outcome (prostate specimen histopathology) reviewed. Any need for adjuvant RT is considered at that time [45]. Evaluation of possible long-term AEs should also be done and treatment, including penile rehabilitation, applied when indicated. Further follow-up at 3, 6, and 12 months are carried out by the urologist or the patients' regular general practitioner (GP) [45].

PCa patients are usually followed by their regular GP for at least 10 years or until high age makes follow-up redundant. Determination of serum PSA, together with disease-specific history, is supplemented by DRE and by imaging studies if locally recurrent disease is suspected [19,45]. A detectable PSA following RP implies residual or recurrent PCa. Usually, the cut-off value in the definition of *biochemical recurrence* (BCR) after RP is set at PSA of $\geq$0.2 ng/ml [45,75].

Adjuvant and salvage treatment following RP

Adjuvant treatment is applied after initial treatment for cancer, to suppress the risk of BCR and metastases. *Salvage treatment* is on the other hand applied after evidence of BCR, as secondary treatment.

Patients, who have undergone RP with positive surgical margins (PSM) and/or invasion of the seminal vesicles, in spite of an unmeasurable PSA postoperatively, have a high risk of local recurrence. They can be offered either immediate RT (*adjuvant RT*) to the surgical bed on recovery of urinary function, or PSA monitoring and *salvage RT* after BCR. Of patients with high-risk PCa in Norway in 2012, 21% had postoperative RT within 300 days of RP, and almost 50% had postoperative RT if there were positive surgical margins in the removed prostate specimen [30]. For intermediate-risk and low-risk PCa, 8% and 4% had postoperative RT, respectively.

The optimal timing and treatment choice for patients with BCR after RP remain controversial however, as the survival benefit for salvage treatments has not been clearly established. Available data indicate that if salvage RT is commenced before PSA reaches 0.5 ng/ml, the oncological outcomes are comparable with adjuvant RT. Adjuvant RT or early salvage RT (PSA <0.2 ng/ml) impose a risk of overtreatment with subsequent increased risk of urethral strictures, urinary incontinence and erectile dysfunction [76]. However, the starting point of salvage RT remains to be set, probably somewhere in the range of PSA 0.2-0.5 ng/ml. Possibly, more complex criteria combining PSA doubling time, Gleason score, and preoperational PSA may be taken into account before initiation of salvage RT in the future.

Adjuvant androgen deprivation therapy (ADT) following RP has always been controversial. It is probably indicated in patients with microscopic lymph node involvement, especially when there are positive surgical margins and seminal vesicle involvement. However, it is not known if patients with only minimal nodal involvement have any benefit of adjuvant ADT [19,45]. In selected patients, only follow-up of PSA, and delayed start of ADT in case of a rising PSA level, is therefore acceptable.

1.2.6. Survival and prognosis

The most relevant outcome measures after curative treatment of localized PCa are PCa-specific and overall survival rates which require at least 10 years of observation time to be meaningful. However, the most commonly reported measure of cancer control following RP has been biochemical recurrence (BCR) (definition of BCR, see p.22).

Two randomized controlled trials comparing radical prostatectomy with watchful waiting have been conducted. *The Scandinavian Prostate Cancer Group (SPCG)-4 trial* was the first to show that RP reduced PCa mortality and risk of metastases compared to WW in patients with clinically localized, low- or intermediate-risk PCa [77]. At 18 years follow-up patients who underwent RP had significantly lower overall mortality (56% vs. 69%, RR=0.71), lower PCa specific mortality (18% vs. 29%, RR=0.56), and lower risk of developing metastatic disease (26% vs. 38% RR=0.57) compared with WW [78]. The benefit was greatest in men under 65 years of age and those with intermediate-risk PCa. The number of patients needed to treat to prevent one death was 8 in the whole cohort and 4 among men under 65. This study began after PSA testing had been introduced into clinical practice but only 5% of men with PCa were diagnosed after a PSA test.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT) also randomized patients to WW or RP [79]. After a mean follow-up of 10 years, there were no statistically significant differences in mortality, overall survival, and PCa-specific survival. Only patients with a pre-treatment PSA >10 or high-risk PCa experienced a significant benefit in overall survival.

Retrospective analyses of men treated during the PSA era have shown good cancer control, but the impact of RP cannot be determined due to the study design and the lack of control groups. Nevertheless, Boorjian et al. reported a 10-year PCa-specific survival of 99.7%, 97%, and 95% after RP for D'Amico low-, intermediate-, and high-risk PCa, respectively, and Hull et al. reported a mean 10-year PCa-specific survival of 97.6% after RP [40,80]. A recent review of RP for high-risk (of various definitions) PCa, showed that RP with extended pelvic lymphadenectomy is associated very good cancer-related outcomes, especially in specimen-confined disease, although often with multimodal treatment [74]. In conclusion, these data have the limitations of retrospective studies, but show that most patients with localized PCa will live many years following RP.

1.3. Adverse effects and quality of life after radical prostatectomy

1.3.1. Assessment of adverse effects and quality of life

General considerations

More knowledge of PCa treatment outcomes is important to both patients and clinicians, since possible long-term adverse effects (AEs) are important for the choice of primary treatment. The concept of outcome assessment after cancer treatment has been expanded from exclusive reliance on objective clinical parameters (PSM rates, time to BCR, survival time, etc.) to a broader assessment that includes patients' subjective evaluation of their physical, mental, and social well-being and overall satisfaction with life as well as self-reported AEs and their impact on quality of life (QOL). Many symptoms and functions are not measurable with laboratory tests or doctors' ratings, and therefore it is necessary to rely on the patients' self-reports. Some examples are role functioning, social functioning, sense of well-being, pain, fatigue, sexual function and impact of urinary incontinence. It is therefore essential to include self-report of AEs and QOL as part of the outcome assessment after treatment of PCa.

There are differences of opinion on what the term QOL actually implies. For many urologists, QOL is the same as AEs (so-called *disease-specific QOL*) [81]. However, other urologists consider QOL and AEs as independent concepts, well aware of the impact of AEs on a patient's degree of QOL (*generic/health-related QOL*).

QOL related to for example urological problems only, focusing on the patients' well-being related to urinary symptoms affecting daily activities, could be referred to as incontinence-related QOL. Such organ-specific evaluation of QOL is different from that of generic or health-related QOL, covering aspects of physical, emotional and mental well-being. This has been increasingly recognized after Litwin introduced generic QOL measurements with the Short Form 36 (SF-36) questionnaire as a supplement to the University of California Los Angeles Prostate Cancer Index (UCLA-PCI, 1995) instrument for patient-reported AEs after treatment for PCa [82].

To conclude on this issue, QOL can be divided into three concepts: *Global QOL* (overall satisfaction with life), *generic QOL* (includes physical, mental, and social well-being), and *disease-specific QOL* (includes AEs after cancer treatment). Moreover, the term *health-related QOL (HR-QOL)* is often referred to when addressing either of the latter two.

The timing at which a survey of QOL and AEs is performed is of great importance and is especially crucial to consider when comparing studies of AEs after cancer treatment. We distinguish between acute, chronic/long-term and late AEs of treatment. The term "late effects" includes AEs appearing more than a year after treatment.

AEs can theoretically be evaluated and measured by an external observer (health care professional or spouse) or by the patient himself. Previously the evaluation of AEs often relied primarily on the physicians' evaluation of symptoms at follow-up visits. However, physician-reported ratings do not include assessment of a wide variety of patient-experienced subjective symptoms affecting the daily well-being. In general, patients report more frequent and severe AEs than their physicians [83,84]. Therefore, since the 1990's *patient-reported outcomes* (PRO) have been increasingly recognized as valid measures of treatment consequences. There is now a general consensus that the assessment of AEs should primarily be based on patient-report rather than physician-report. *Patient-reported outcome measurements* (PROM) are nowadays part of routine assessment in clinical cancer research to provide added value to traditional clinical outcomes [85-87].

There are several instruments available designed to evaluate patients' function and bother in relation to PCa treatment, but there is currently no consensus as to the best instrument or method for evaluating changes from baseline (pre-treatment) to post-treatment. *Clinical significance* is therefore not a given fact when using PROM but is important to consider when analyzing and interpreting PROM data and measuring changes. The question of how much *change* for a single patient or *difference* between treatment outcomes is considered to be statistically *and* clinically significant is still unanswered. The FDA guidance [88] has moved away from recommending the use of the 'minimally important difference' [89]. Other guidelines propose that a change of 10 points on a 0–100 scale is a sufficient change to have clinical meaning [90,91]. This magnitude is about the same as the 0.5 standard deviation (SD) that has been suggested as being universally acceptable [92].

Measuring effect size (ES) is a different approach to analyze and interpret differences/changes into clinical significance. Cohen considered ES values ≥0.40 as clinically significant when group means are compared [93,94].

Questionnaires

The *University of California Los Angeles Prostate Cancer Index* (UCLA-PCI) questionnaire with 20 items was specifically developed to assess typical AEs after treatment for PCa [82]. The *Expanded Prostate Cancer Index Composite* with 50 items (EPIC-50) is a modified and extended version of the UCLA-PCI and includes items to capture additional concerns relevant to RP, RT, and androgen deprivation [95]. Later an abbreviated version with 26 items has been developed (EPIC-26) [96]. The EPIC questionnaires rate the patients' experiences of urinary, sexual, bowel, and hormonal functions, and bother (problems) related to each specific function, and overall problems.

Other examples of instruments assessing AEs after PCa treatment are the European Organization for Research and Treatment of Cancer PCa module (EORTC QLQ-PR25), the Prostate Cancer Symptom Scale (PCSS, formerly named QUFW94) and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) [97].

The EPIC questionnaires were recently assessed as the best questionnaires available regarding the evaluation of AEs in PCa patients [98]. The *International Consortium for Health Outcomes Measurement (ICHOM)* recently published guidelines for localized PCa where the EPIC-26 is the recommended instrument for assessment of AEs. The recommended timing is before and 6 months after PCa treatment and then annually up to 10 year follow-up [99].

The abovementioned AE-specific instruments are often combined with generic QOL instruments [100]. Litwin introduced generic QOL measurements with the Short Form 36 (SF-36) together with his UCLA-PCI instrument. The SF-36 is intended to measure "general health concepts not specific to any age, disease, or treatment group" [101].

Later, the SF-36 was supplemented with the shorter SF-12 that contains physical and mental composite scores, as expression of the two different aspects of QOL [102]. The SF-12 is the instrument recommended for the rating of generic QOL in PCa patients based on its good psychometric properties [97] and should ideally be assessed simultaneously with the EAs, before and after treatment.

1.3.2. Common adverse effects after radical prostatectomy

RP is followed by a specific pattern of persisting "typical" AEs that may become long-term AEs lasting more than a year after RP. The most frequent and bothersome AEs are erectile dysfunction (ED) and urinary incontinence, which are considerably more common than after RT [2,103-105]. Other sexual and urinary dysfunctions than ED and incontinence may also occur.

For patients who have undergone RP, generic QOL and chronic fatigue are probably in the range of the normal population, and better than patients who have undergone RT [104,106-108]. However, it has been shown that AEs after RP have a negative impact on generic QOL [103,109]. And for some patients, persistent urinary incontinence negatively influence their work life [110,111].

Urinary adverse effects

RP may cause damage to the bladder, urethra and surrounding tissue, including blood vessels and nerves. Patients with PCa and an enlarged prostate may have urinary symptoms before RP, usually *obstructive symptoms* like weak flow, incomplete emptying, post-micturition dribble, and *irritative symptoms* like frequency, nocturia, urgency and urgency urinary incontinence (UUI). The prevalence of incontinence before RP has been shown to be 13% and the prevalence of irritative/obstructive symptoms 36% [112,113] After RP, any previous obstructive symptoms are likely to be replaced by storage symptoms in the form of stress urinary incontinence (SUI). Irritative/obstructive symptoms may prevail or be relieved following RP, probably depending on the degree and duration of any previous obstruction [5].

Following removal of the prostate and anastomosis of urethra and bladder neck during RP, patients have an indwelling catheter for 1-2 weeks. Immediately after catheter-removal there is a high rate of urinary incontinence, which improves gradually over the next 12-24 months. The most significant improvement occurs three months following surgery [112].

Postprostatectomy incontinence (PPI) is the most frequent urinary AE, caused by intrinsic sphincter deficiency (ISD) mostly, and/or detrusor overactivity (DO) in some cases. Patient-reported PPI ('any urinary leakage') is present in up to 87% of patients after RP, and persistent long-term PPI has been reported in 40% [114,115].

Advancing age is an established risk factor for PPI, but there is some controversy to whether comorbidity, high PCa stage, lack of nerve sparing, or blood loss are associated with the risk of PPI [115]. Other potential risk factors include high BMI, low socioeconomic status,

non-black race, high education level, high PSA, high Gleason score, high prostate volume, and preoperative incontinence and erectile dysfunction [67,115-117]. Men who undergo salvage surgery or salvage RT for recurrent PCa have a higher risk of incontinence [118].

Conservative management of PPI includes lifestyle interventions, pelvic floor muscle training (PFMT) with or without biofeedback, and bladder training [67]. In patients with symptoms of bladder dysfunction, additional anticholinergic medication is the recommended first-line treatment for early PPI. For persistent, severe PPI after conservative treatment has failed, surgical treatment is available. Up to 10% of patients with PPI will need surgical treatment of their urinary leakage [67]. Put in another way, the proportion of patients following RP requiring surgery for PPI is 5%-9% [114,115,115,119].

Long-term urinary AEs, definitions, assessment, and treatment, will be discussed in more detail later (Chapter 1.3.3.-1.3.5.).

Sexual adverse effects

Sexual AEs after RP are complex, as sexual function depends on both physiological and psychological factors. Individual factors like age, education, comorbidity, diabetes mellitus, BMI, general health, preoperative sexual function, as well as partner-related factors influence postoperative sexual function and the subjective experience of sexual bother [120-122]. As many as 45%-64% of RP candidates suffer from erectile dysfunction (ED) preoperatively [122]. Other potential risk factors for sexual AEs, apart from treatment modality and nerve sparing during RP, include advanced PCa stage and high PSA prior to treatment [121-123].

Considering only preoperatively potent patients, recovery of erectile function with nerve-sparing procedures one year after RP varies between 31% and 90% [121,122,124,125]. Norwegian studies have shown that 60%-90% of PCa patients have ED following RP, disregarding nerve-sparing technique [126,127].

Recovery of erectile function may be slow over the course of more than two years [63,122]. *Penile rehabilitation strategies* have been developed with the goal of increasing the probability and speed of return of erectile function [128]. Regular administration of per oral phosphodiesterase type 5 (PDE-5) inhibitors, creation of erections with vacuum devices, or intracavernosal injection of vasocative agents (papaverine-phentolamine, alprostadil) improves the probability of recovering erectile function, probably by preventing prolonged

ischemia thereby preserving the smooth muscle tissue and function of the corpora cavernosa [128-130].

In Norwegian national PCa guidelines this aspect of follow-up is hardly mentioned [45]. Most urological departments have some form of local guidelines on penile rehabilitation, although these are followed to varying degrees.

Quality of life (QOL)

There is conflicting evidence in the literature regarding the impact of PCa treatments and AEs on QOL. AEs after treatment for PCa, such as urinary and sexual dysfunction, which is associated with reduced *disease-specific QOL*, can also have an impact on *generic QOL*. Generic QOL assessments of the AEs following RP have shown, in the past, that major domains such as physical, emotional and social functioning seem not to be affected or to recover within a short time after RP [107]. However, in their large Prostate Cancer Outcomes Study (PCOS), based on the Surveillance, Epidemiology, and End Results (SEER) program, Penson et al. showed that AEs, such as urinary function and bother, and sexual function and bother, were independently associated with reduced generic QOL [109].

A recent systematic review of QOL outcomes following RP report similar or improved general QOL (using the SF-36), and no observable difference between men undergoing RP, RT, men electing AS, and control subjects [122].

1.3.3. Pathophysiology of urinary dysfunction following radical prostatectomy

The lower urinary tract has two missions: protecting the kidneys while maintaining a social function, both of which involve well-functioning storage most of the day and periodic voiding at the right time and place. The storage and voiding of urine depend on the coordinated activity of smooth and striated muscles in the two functional units of the lower urinary tract, the bladder and the outlet (in males consisting of the bladder neck, the prostate, the urethra, and the urethral sphincter). In the healthy male, all parts of the outlet are important for the continence mechanism, along with a normal bladder function. The lower urinary tract is different from other internal organs under autonomic control in that it has only two modes of operation: storage and voiding, i.e. activity that is turned on or off, not a continuous tonic pattern like the GI tract or cardiovascular system [131].

Hence, based on these two modes, lower urinary tract dysfunction (LUTD) has traditionally been divided into two major categories; dysfunctional storage/filling phase and dysfunctional voiding phase. *Dysfunctional storage* can be characterized by incontinence or so-called irritative/obstructive symptoms like urgency and frequency. *Dysfunctional voiding phase* with slow and/or incomplete emptying of the bladder can be caused by an underactive detrusor or bladder outlet obstruction. (The latter will not be commented to depth in this thesis.) In addition, *post-micturition symptoms* are sometimes referred to as a third category.

Urinary dysfunction following RP can comprise all of the above. Thus, as mentioned briefly previously, *postprostatectomy incontinence* (PPI) is potentially caused by either intrinsic sphincter deficiency (ISD), detrusor overactivity (DO), or both. Classically, ISD is associated with the symptom of stress urinary incontinence (SUI) and DO is associated with the symptom of urgency urinary incontinence (UUI). Although incontinence may well be present before RP, preoperative incontinence is usually characterized by UUI and/or post-micturition dribble, due to DO and incomplete emptying secondary to obstruction, rather than SUI due to ISD.

ISD can be caused by damage to the urethral sphincter through direct injury, or injury to the nerve supply or the supporting structures. The bladder neck and the prostate are important contributors to the continence mechanism and are damaged and extirpated during RP. Along with direct and/or indirect damage to the urethral sphincter, supporting structures, blood supply and nerves, ISD may be the result. Reduced blood flow to the urethra is associated with a lower urethral pressure [132,133], which in turn is associated with ISD [134].

These damages can cause 'urethral hypermobility' as well as 'true intrinsic sphincter deficiency' of the rhabdosphincter [134]. The 'hypermobility' is a displacement of the urethra during sudden increase in abdominal pressure which decreases pressure transmission, a theory not completely free from controversy [135]. 'True' ISD is when the urethra is unable to generate enough outlet resistance to keep the urethra closed at rest or with minimal physical activity [134].

Bladder dysfunction after RP may be represented not only by DO, but also by low bladder compliance and/or impaired detrusor contractility (detrusor underactivity). However, bladder dysfunctions may be present without giving any symptoms, especially if present together with ISD [136].

Although there is extensive literature on urinary incontinence after RP, there is little data on bladder function after RP. Bladder dysfunctions may occur de novo following bladder denervation during surgery, be induced by pre-existing long-term bladder outlet obstruction, or be a consequence of bladder ageing [137]. Most published reports agree that DO may aggravate PPI, but rarely is the primary cause of PPI. However, it is not clear whether the anatomic dissection during surgery affects both the storage/filling phase and the voiding/micturition phase.

Irritative/obstructive symptoms, i.e. symptoms indicative of bladder dysfunction or obstruction (prostate enlargement preoperatively, anastomosis stenosis postoperatively), usually improve after RP. Lepor and Kaci were the first to show that patients with irritative/obstructive symptoms before RP have a moderate improvement one year after RP [112]. Others have shown the same effect lasting for up to five and ten years after RP [138].

The wide anatomic dissection around the prostate during surgery can damage the afferent and efferent innervation of the trigone, rhabdosphincter, bladder neck, and posterior urethra, with resulting insufficiency of the continence mechanism and partial denervation of the detrusor muscle [5]. Modifications of the surgical techniques and postoperative patient care have been proposed in an attempt to improve the continence rates after RP.

The nerve sparing technique by Walsh for preservation of erectile function, popularized in the 1990's, produced early data indicating that the technique may also result in improved rates of continence by preserving neural innervation to the rhabdosphincter at the time of RP [68,139,140]. Continence nerves contained in the neurovascular bundles can be damaged by blunt dissection with clamping of posterior periurethral tissues beneath the

urethra at the prostatic apex, and sutures placed at the 5 and 7 o'clock positions for vesicourethral anastomosis [11]. Moreover, dissection of the seminal vesicle can injure the pelvic nerve plexus, which is located on the lateral surface of the rectum with its midpoint at the tip of the seminal vesicles and provides autonomic innervation to all pelvic organs.

Finally, to preserve urinary continence after RP, preservation of the entire circumferential rhabdosphincter musculature and the fascial tissues, especially giving attention to restoration of the posterior aspect of the rhabdosphincter and to the innervation of both the rhabdosphincter and the mucosal and the smooth muscle components have been suggested [11,12,141]. In 'posterior reconstruction', the posterior rhabdosphincter is joined to the posterior Denonvilliers' fascia and fixed to the bladder wall 1-2 cm cranial to the new bladder neck to avoid caudal retraction of the sphincteric complex, prior to completing the standard vesicourethral anastomosis [12,12,142]. This technique was first described by Rocco et al. in 2001, and served as a basis for newer additional modifications [63].

Further advances and suggestions include anterior reconstruction/suspension, fascial sling construction, bladder neck preservation, intraoperative cooling, and pubovesical complex-sparing [63]. However, as we still lack international consensus on standardization of outcome definitions (such as continence), the effect/benefit of these recent modifications have been difficult to document and have therefore been somewhat controversial.

1.3.4. Terminology and assessment of urinary dysfunction

Assessment of urinary dysfunction can be done with several methods:

1) By self-report (standardized questionnaires) assessing symptoms and related bother.
2) A focused clinical history using standardized terminology [143] can provide a great deal of valuable information and details.
3) Urinary diaries and pad tests give an indication of the severity of the urinary dysfunction(s).
4) Non-invasive clinical examinations such as free uroflowmetry and ultrasound for post-void residual urine measurement.
5) Invasive clinical methods including urodynamics and cystoscopy.

Patient reported urinary symptoms

The International Continence Society (ICS) published an updated version of 'The Standardisation of Terminology of Lower Urinary Tract Function' in 2002. The report presented definitions of symptoms, signs, urodynamic observations and conditions associated with lower urinary tract dysfunction (LUTD) and set the gold standard of terminology in the field [115,143,144]. A short review was published in 2009 [145].

Urinary incontinence is defined by ICS as 'the complaint of any involuntary leakage of urine' [143]. The most common definition of incontinence following RP used in the medical literature though, is 'any use of pads' [146]. However, this definition excludes patients who report any leakage (without pad use), which can be a significant proportion of patients who have undergone RP. Up to 50% of men who do not use pads have occasional leakage of urine after RP [115,147]. Herschorn et al. have presented three definitions of urinary continence [115]:

1) Total control/perfect continence.
2) Occasional leakage but no pad.
3) Less than one pad/no or one (0-1) pad per day.

These definitions of different levels of leakage are commonly used when reporting continence and/or incontinence following RP. The differences in definitions contribute to the wide variety in reported prevalence rates of PPI [3,4]. Liss et al. (2010) proposed that continence should be strictly defined as *no pads*, not *0-1 pad*, based on their findings that patients who use pads, even just one 'security pad', have significantly lower QOL compared with patients who do not use pads at all [148]. However, when comparing correspondence among continence

definitions (using the UCLA-PCI questionnaire), Krupski et al. found that only 42% of patients who reported using no pads did not leak urine at all [4].

Validated symptom scales with several items of objective (pad use) and subjective (bother) experience, like the EPIC-26, may be useful when grading PPI, as several different aspects are considered [82,149]. However, there is not yet international consensus regarding stratification or grading of urinary incontinence into mild, moderate and severe forms.

Some authors have proposed 'severe incontinence' to be the same as 'total incontinence' with reported rates of 5% to 10% after RP, increasing with age [150]. The proportion of patients requiring surgery for PPI following RP is another measure of the prevalence of 'severe PPI', and the proportion has been reported to be between 5% and 9%, but a source of error could be that some patients may never have been offered surgical treatment [114,115].

Urinary incontinence can be divided into different types. *Stress urinary incontinence* (SUI) is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [143]. The symptom of SUI has shown a positive predictive value of 95% and a negative predictive value of 100% regarding ISD [136].

Urgency urinary incontinence (UUI) is the complaint of involuntary leakage accompanied by or immediately preceded by urgency [143]. The symptom of UUI has shown a positive and negative predictive value of 44% and 81%, respectively, regarding DO [136].

Mixed urinary incontinence is a combination of SUI and UUI. Post-micturition dribble describes the involuntary loss of urine immediately after urinating. Nocturnal enuresis is the complaint of loss of urine during sleep [143].

Following RP, other urinary symptoms than incontinence may be present. Additional storage symptoms include urinary frequency, nocturia, and urgency. Voiding symptoms include slow stream, hesitancy, straining, and terminal dribble. Post-micturition symptoms include the feeling of incomplete emptying and post-micturition dribble [143].

Urinary diary and pad weighing test

Urinary diaries, also known as voiding or bladder diaries, are useful tools when evaluating urinary function and urinary incontinence. ICS has defined the following three types of urinary diaries on the basis of the recorded parameters [143]:

1. *Micturition time charts* record only the times of micturition, day and night, for at least 24 hours.
2. *Frequency-volume charts* record the volumes voided and the time of each micturition, day and night, for at least 24 hours.
3. *Bladder diaries* record the times of micturition and voided volumes, as well as other information, such as incontinence episodes, pad usage, fluid intake, degree of urgency, the degree of incontinence, and precipitating activities.

Urinary diaries have been commonly used and recommended in the assessment of patients with lower urinary tract symptoms. Many patients have poor insight into their voiding habits, and a bladder diary provides the most objective, reliable, and reproducible means to analyze the historical aspects of the incontinence; elucidating the frequency and volume of voids, functional bladder capacity, and the activities that cause urinary incontinence – the latter being an important factor in determining the treatment choice. Recently Bright et al. developed and validated a urinary diary for the first time [151].

The grade of the urinary leakage can be objectively quantified by a *standardised pad weight test* as recommended by the ICS [143]. The 24-hour pad test is the most accurate, objective and reproducible test for quantification of incontinence [115,152-154]. The test has excellent correlation with the subjective patient assessment of the degree of incontinence and is the most widely used [153]. However, a graded severity scale based on the 24-hour pad test has not yet been established for men.

Urodynamics

The term 'urodynamics' encompasses any investigation of lower urinary tract dysfunction from the simple to the sophisticated, and include voiding diary and pad testing, as mentioned above, free uroflowmetry and ultrasound for post-void residual urine estimation, and invasive urodynamics [155]. However, generally the term 'urodynamics' has become synonymous with invasive urodynamics. All definitions below are obtained from the ICS reports and associated documents [134,143,145,156-158].

The aim of clinical urodynamics is to reproduce symptoms while making precise measurements in order to identify the underlying causes for the symptoms, and to quantify the related pathophysiologic processes [158]. In that way it is possible to guide treatment correctly in relation to the patients' symptoms. Bladder dysfunction may be demonstrated with urodynamic investigation even in the absence of signs and symptoms reported by the patients. Thus, urodynamics represent the only method to accurately diagnose causes of incontinence and any other dysfunction during the storage or voiding phases.

Urodynamics may be divided into non-invasive urodynamics (catheter-free uroflowmetry) and invasive urodynamics (filling cystometry and pressure-flow study of voiding).

Free uroflowmetry is a simple and non-invasive way of understanding both storage and voiding symptoms. Estimation of post-void residual urine by ultrasound completes the non-invasive assessment of voiding function. Documentation of a maximum urinary flow rate (Qmax), voided volume, duration of voiding and the shape of the flow curve during a representative flow as well as the post-void residual give useful information.

- *Bladder voiding efficiency (BVE)* is a product of bladder contractility against urethral resistance and is measured according to the degree of bladder emptying:

  BVE = (voided volume/total bladder capacity) x 100

  There is no defined pathological cut-off, although no post-void residual urine and a BVE of 100% is normal.

However, a reduced flow rate on the uroflowmetry cannot distinguish between obstruction and poor detrusor contractility. As the voiding function reflects the interaction between the relaxed outlet and the contracting detrusor, variation of both will affect the flow [158].

Invasive urodynamics consists of two parts: the filling cystometry (simulating and measuring the filling phase) and the pressure-flow study (simulating and measuring the voiding phase) [158]. During *filling cystometry*, the bladder is filled with isotonic saline, usually in the rate of 20-60 ml/min, simulating the physiologic filling of the bladder. Physiologic filling rate is defined by the ICS as body weight (kg) divided by four, expressed as ml/min (for example 80/4=20 ml/min). Bladder sensations are recorded and evaluated as normal or not. Detrusor overactivity (DO) and reduced compliance may be observed, in contrast to a normal filling phase with stable detrusor pressure (little or no change). Incontinence related to DO or related to increased abdominal pressure may be observed during filling cystometry [158].

- *Detrusor overactivity (DO)* is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase [143].
- *Bladder compliance(C)* describes the relationship between change in the bladder volume (ΔV) and change in detrusor pressure (ΔPdet) [143]:

  C = ΔV / ΔPdet

  C ≤20 ml/cmH_2O is defined as impaired/poor compliance.
- *Detrusor overactivity incontinence* is defined as urgency incontinence because of an involuntary detrusor contraction [143].
- *Urodynamic stress incontinence* is defined as an involuntary leakage of urine during increased abdominal pressure in the absence of a detrusor contraction [143].
- *The abdominal* or *Valsalva leak point pressure* (ALPP/VLPP) is defined as the intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction [143]. The ALPP can be useful in the assessment of *degree of ISD* and when considering treatment choices for SUI [159]. According to Abrams an ALPP ≤60 cmH_2O implies *intrinsic sphincter deficiency* (ISD) [134]. However, there are several problems related to the measurement of ALPP, regarding patient compliance and position, bladder volume, the indwelling catheter, moment of measurement etc [115]. Therefore, that parameter has limited value in the clinical setting.
- *The maximum urethral closure pressure* (MUCP) can be assessed by urethral pressure profilometry during filling cystometry and is an assessment of urethral function. The MUCP is defined as the maximum difference between the urethral pressure and the intravesical pressure [143]. The urethral pressure is the fluid pressure needed to just open a closed urethra [143]. According to Abrams an MUCP ≤20 cmH_2O is equivalent to an

ALPP ≤60 cmH_2O, implying ISD [134]. However, there are also problems with the MUCP as there is a large overlap with normal continent people. Urethral pressure profilometry alone is not satisfactory for the diagnosis of urodynamic stress incontinence [160].

In the *pressure-flow study*, voiding is assessed by measuring urine flow rate and voiding pressures, and studying their relationship [156,158]. Nomograms, including the quite similar Abrams-Griffiths nomogram, the Schäfer nomogram and the most recent ICS nomogram, can be used to categorize patients' bladder contractility and outlet [156].

- *Detrusor underactivity* is defined as a contraction of reduced strength and/or duration causing slow or incomplete emptying of the bladder [143]. One way of measuring detrusor contractility is by the bladder contractility index, BCI [156].

  BCI = Pdet@Qmax + 5 x Qmax

  where *Pdet@Qmax* is the maximum detrusor pressure at maximum flow rate (*Qmax*). BCI <100 indicates weak contractility.

- *Bladder outlet obstruction* is characterised by increased detrusor pressure and reduced urine flow rate [143]. The bladder outlet obstruction index, BOOI, is calculated as follows [156]:

  BOOI = Pdet@Qmax – 2 x Qmax

  BOOI > 40 is obstructed, 20-40 is equivocal, and < 20 is unobstructed

The abovementioned nomograms and indices, BCI and BOOI, were originally validated for men with an enlarged prostate, and have not been validated in men without a prostate. After RP the urethra offers little resistance to micturition, thus low detrusor pressures are sufficient for a normal urinary flow rate [161]. Thus, the standard urodynamic classifications in nomograms and by indices may be misleading in prostatectomized men. However, they are frequently used in lack of something better [137].

Urodynamic studies after radical prostatectomy

Few studies have compared urodynamic findings before and after RP [5,137,137]. The review by Porena et al. (2007) presented nine prospective studies comparing preoperative and postoperative urodynamic data (Table 3) [137]. Results on bladder dysfunction after RP varied widely and the role of RP in the development of bladder dysfunction was controversial [137]. In most prospective studies DO was associated with other urodynamic dysfunctions.

ISD was by far the most common finding in men undergoing urodynamics for PPI [136,137,161]. Coexisting urodynamic bladder dysfunction (reduced bladder compliance, detrusor overactivity, impaired detrusor contractility) was present in 9% - 88% of the patients after RP [137]. Urodynamic bladder dysfunction was presented as the sole diagnosis in 0% to 100%, with DO in 0% to 40%, while ISD was presented as sole diagnosis in 2% to 71%. Impaired detrusor contractility (26%-33%) and reduced bladder compliance (1%-59%) have traditionally been thought to resolve within 8 months after RP [137].

Table 3. Characteristics of the studies and bladder dysfunctions after RRP [137]

Authors, year	Type of study	No. of patients	Follow-up	DO	RBC	Impaired detrusor contractility	BOO	SUI	SUI *and* bladder dysfunction
Hellstrom et al, 1989	P	19[a]	6	—		19 (100)	—	—	—
Presti et al, 1990	R	24[b]	60	6 (25)[c]	—	—	—	—	—
Foote et al, 1991	R	71	40	0 (0)	5 (7)	—	—	25 (35)	29 (41)
Foote et al, 1991	P	26	12	—	—	—	—	8 (33)	17 (67)
Constantinou and Freiha, 1992	P	13	23	8 (62)[d]	—	—	—	0	—
Leach and Yun, 1992	R	71	12	0 (0)	8 (12)	—	—	26 (37)	22 (31)
Goluboff et al, 1995	R	25	37	10 (40)	2 (8)	—	—	2 (8)	13 (52)
Sasaki et al, 1995	P	25	12	—	5 (20)	—	—	—	—
Leach et al, 1996	R	25[e]	36	1 (4)	3 (12)	—	—	8 (32)	12 (48)
Minervini et al, 1996	P	39	6	12 (31)[c]	—	—	—	—	—
Hammerer and Huland. 1997	P	82	6	33 (41)[c]	—	—	—	—	—
Ficazzola and Nitti, 1998	R	60	13	5 (8)	0	—	5 (8)[f]	32 (53)	22 (37)
Winters et al, 1998	R	65	59	1 (1.5)	—	—	—	46 (71)	18 (28)
Kleinhans et al, 1999	P	44	7.6	3 (6.8)	—	—	—	1 (2.3)	0 (0)
Groutz et al, 2000	R	83	32	3 (4)	—	1 (1.2)	1 (1.2)	26 (32)	73 (88)
Giannantoni et al, 2004	P	49	8	—	—	—	—	—	32 (65)
Huckabay et al, 2005	P[g]	60	32	24 (40)[c]	—	—	8 (13)	35 (58)	25 (42)
Kielb and Clemens, 2005	R	146	49	1 (0.7)	14 (10)	48 (33)	19 (13)	95 (65)	44 (30)
Majoros et al, 2006	P	63	2	11 (17)	1 (1.6)	2 (3)	3 (5)	38 (60)	6 (9)

Data are shown as number of patients, number of months, or n (%).
RRP=retropubic radical prostatectomy; DO=detrusor overactivity; RBC=reduced bladder compliance; BOO=bladder outlet obstruction; SUI=stress urinary incontinence; R=retrospective study; P=prospective study; — =not reported.
[a] Seven patients had a previous transurethral resection of the prostate (TURP). [b] Four of 24 incontinent patients and 1 of 13 continent patients previously underwent TURP; 1 of 24 incontinent patients previously underwent radiotherapy and hormonal therapy. [c] The authors did not specify if DO was associated with other dysfunctions. [d] Seventy-eight percent of patients were overactive before surgery. [e] Twenty-four patients had RRP, and 1 had perineal prostatectomy. [f] Three of 5 patients complained of DO. [g] Without preoperative urodynamics.

Later, Giannantoni et al. (2008) compared urodynamic status in 54 patients before and after RP. They found DO in 61% of patients before RP and 70% eight months after RP ($p>0.05$), which indicated that surgery may be the cause of DO in a small percentage of patients (9%). Among the patients with normal detrusor function preoperatively 30% had weak detrusor contractility postoperatively. Regarding abnormalities directly related to the long-term consequences of an obstructing prostate before RP, the presence of bladder outlet obstruction (BOO) decreased from 59% before RP to 7% after RP ($p<0.001$), and DO together with BOO decreased from 35% to 3% ($p<0.001$). The presence of DO and weak detrusor contractility together increased from 17% to 39% ($p=0.05$). ISD was not found in anyone before RP and in 74% after RP ($p<0.001$).

Among the 32 patients followed for 36 months after RP, 56% had DO, de novo in 16%. Impaired bladder compliance was present in 28%, de novo in 16%, and weak detrusor contractility in 25%, de novo in all. ISD was present in 59%, de novo in all.

In that study detrusor contractility was evaluated by the Schäfer nomogram, which may overestimate hypocontractility in a prostatectomized population, as mentioned above. Nevertheless, a high proportion of patients had long-term urodynamic abnormalities following RP, including both dysfunctions that developed de novo and that also had been present preoperatively.

In conclusion, there are a few good studies comparing urodynamics before and after RP, mostly showing that several dysfunctions are often present simultaneously. However, due to diverging results in these studies it is hard to conclude on the pathogenesis of the bladder dysfunctions, whether the factors are pre-existing or develop de novo following surgery.

Urodynamic studies before incontinence surgery

Urodynamic investigation is recommended in the evaluation of PPI, especially prior to surgical treatment [67,115,115,157,162-164]. This recommendation is not evidence-based however [165,166]. Previous studies, although few, have not been able to show that urodynamics can predict outcome of PPI surgery [167-169].

Bladder dysfunctions, especially detrusor overactivity and underactivity, have traditionally caused some concern when planning PPI surgery. The hypothesis has been that detrusor overactivity may potentially be aggravated with partial obstruction caused by an artificial urinary sphincter (AUS) or a sling, while detrusor underactivity may lead to

incomplete bladder emptying in such a situation. However, no studies have been able to confirm that. Thiel et al. retrospectively studied 86 patients with AUS for PPI [168]. The presence of detrusor overactivity or reduced bladder compliance in patients before PPI surgery did not predict AUS failure (>1 pad/day). In a prospective study of 40 patients after RP, Trigo-Rocha et al. did not find significant associations between urodynamic bladder dysfunctions (detrusor overactivity, impaired detrusor contractility, reduced bladder compliance) and worse surgical outcome (>1 pad/day) [169]. Gomha and Boone, however, found in a study of 86 patients that poor bladder compliance was associated with persistent urgency and urgency incontinence after AUS implantation [170].

Only patients with AUS implantations, not slings, had been studied in this respect.

1.3.5. Treatment of postprostatectomy incontinence

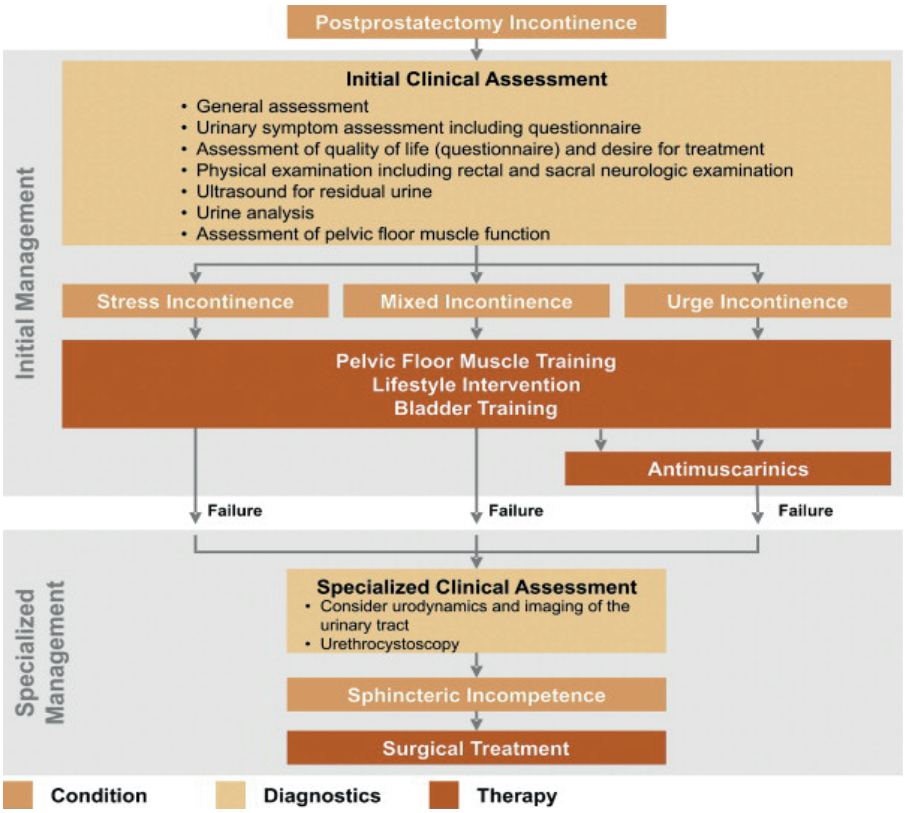

Figure 6. Initial and specialized management of PPI based on EAU 2010 guidelines [67]
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Overview

Contemporary management of PPI is summarized well by Bauer et al. (Figure 6) [67]. They advocate an initial two-step assessment. The first concerns evaluation of symptoms, urine analysis, residual urine, QOL, grade (amount) of stress incontinence and assessment of pelvic floor muscle function. In a second step, it is recommended that all patients then undergo pelvic floor muscle training, lifestyle intervention and bladder training. Those with urgency urinary incontinence (UUI) should be treated with anticholinergic medication, α1-adrenoceptor blockers, or a combination [171]. Some of those with mild stress urinary

incontinence (SUI) who are reluctant to undergo surgical treatment can *theoretically* be treated with Duloxetine, a serotonin-norepinephrine reuptake inhibitor, although the usage of Duloxetine for SUI is off-label and not applied in Norway [171]. In those who fail conservative treatment, specialized management with endoscopic and urodynamic evaluations are recommended. However, there is no definite statement to the effect of such evaluations.

In patients with persistent SUI, surgical treatment is recommended after initial conservative therapy has failed or is insufficient [67,115]. Well-established surgical treatment options for PPI include urethral slings and the artificial urinary sphincter (AUS). A common view is that patient's demands for minimally invasive treatment options are high and will drive the choice to use a sling to avoid using a mechanical device such as the well-established AUS [67]. Other options include urethral bulking agents and the adjustable balloon system, both of which have not shown as promising results as the AUS and the slings, and are not primarily recommended for PPI [67,67,115,157]. Transurethral injection of autologous muscle stem cells to reconstitute the deficient urethral sphincter has been introduced but the efficacy has yet to be established [172].

Surgical interventions after failed conservative therapy for DO include intradetrusor injection of Botulinum Toxin A, sacral nerve stimulation/modulation, and enterocystoplasty/urinary diversion [162]. These topics will not be covered in this thesis.

The most recently published 'EAU Guidelines on Surgical Treatment of Urinary Incontinence' (2012 and Update in 2014) have based their recommendations on three recent literature reviews on the subject by Herschorn et al., Abrams et al., and Bauer et. al [67,115,157]. Their recommendations are summarized below [162]:

Urethral slings

There are two types of male urethral slings for SUI available; fixed and adjustable. Fixed slings (vide infra) are positioned under the bulbar urethra and introduced and fixed by a retropubic or transobturator approach, while the adjustable slings (Remeex®, Argus®, ATOMS®) can be adjusted postoperatively. Available evidence indicates that the fixed slings seem superior to the adjustable slings [162].

For the fixed slings, two therapeutic concepts are proposed for continence restoration: Urethral compression (InVance®, TOMS®, Argus®) and repositioning of the urethral bulb (AdVance®, Figure 7). Published reports indicate that fixed slings cure or improve PPI for at

least three to five years and are less effective for men with severe incontinence (>400g/24h), previous RT, or previous urethral stricture therapy [144,172].

The InVance® is a bone-anchored perineal sling that has been evaluated quite extensively with success rates of 40%-88% with follow-up of up to 48 months [115,173]. Due to high complication rates and low success rates, the sling has been removed from the market in some countries [172].

The AdVance sling (Figure 7) is a retrourethral transobturator sling and has reported success rates of 76%-91% with follow-up of 12-36 months [115]. The most common adverse events reported are urinary retention (3%-21%) and perineal pain (0-20%). Rare adverse events include compartment hematoma, worsening of urinary incontinence and urethral perforation [115]. Despite continued patient satisfaction, it has been shown that patients use an increasing number of pads/day as time advance from the sling procedure [174].

At OUH Rikshospitalet, the AdVance sling was introduced in 2009.

Artificial urinary sphincter

The artificial urinary sphincter (AUS) AMS800® has been used for the treatment of SUI for almost 40 years [175]. This device restores continence with an occlusive cuff around the bulbar urethra (or the bladder neck) and a corresponding pump (opening switch) that is implanted subcutanously in the scrotum (Figure 8). The AMS800® was introduced at OUH Rikshospitalet in 1983 and was initially mostly used for treatment of neurogenic SUI, and rarely for PPI.

Although the AMS800® is considered to be the gold standard treatment for men with SUI, the level of evidence is low for this statement [162]. There have been no well-designed randomized controlled trials comparing the abovementioned surgical options for SUI in men. Cohort studies suggest that AUS implantation is effective for cure and improvement of SUI in men, although long-term device failure is common and patients should be informed that there is a high risk of needing revision/replacement after 5-10 years [172]. Previous pelvic radiotherapy does not appear to affect the outcome of AUS implantation. Tandem-cuff placement (two cuffs around urethra) has been tried to improve continence rates, but has not been shown to be superior to single-cuff placement.

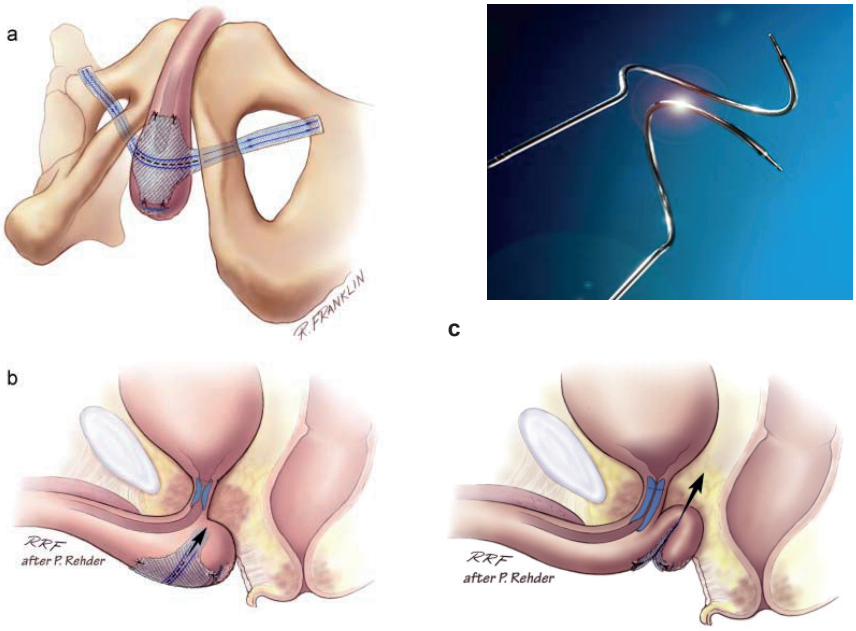

Figure 7. a) The AdVance ® sling is a retrourethral transobturator sling inserted from the perineum by helical introducer needles. b) and c) The postulated mode of action is a repositioning of the bulbar part of the urethra into the pelvic floor [176].
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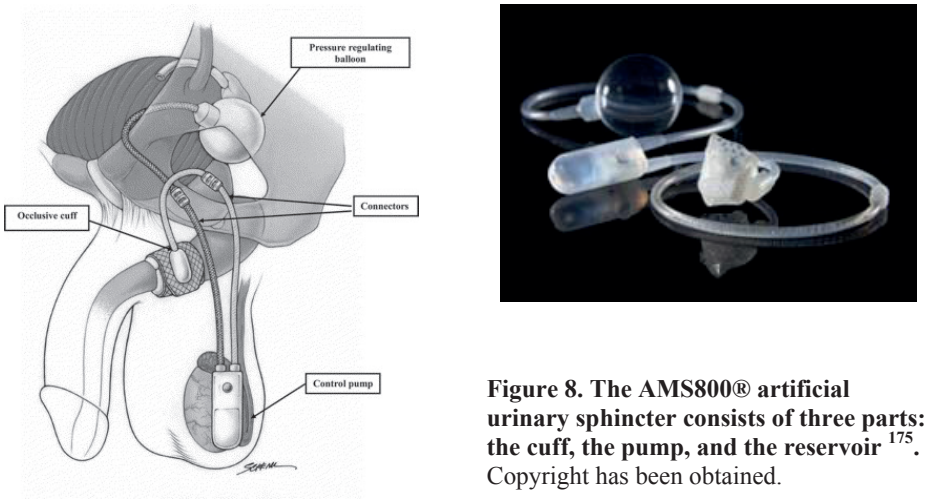

Figure 8. The AMS800® artificial urinary sphincter consists of three parts: the cuff, the pump, and the reservoir [175].
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The proportion of patients who continue to experience treatment success (measured by requiring 0-1 pads per day) after implantation of an AUS ranges from 59% to 90%, with mean up to 11 years follow-up [115] (Table 4). High satisfaction rates of 87%-90% are reported, even without total continence [115].

Table 4. Results of the artificial urinary sphincter in postprostatectomy incontinence [115] Copyright has been obtained.

Author, year	No. pts.	Follow-up (yrs)	0-1 pad/day
Goldwasser et al., 1987	42	1.2	82%
Montague, 1992	66	3.2	75%
Perez and Webster, 1992	49	3.7	85%
Martins and Boyd, 1995	28	2	85%
Fleshner and Herschorn, 1996	30	3	87%
Haab et al, 1997	36	7.2	80%
Klijn et al., 1998	27	3	81%
Mottet et al., 1998	96	1	86%
Madjar et al., 2000	71	7.7	59%
Lai et al., 2007	218	3.1	69%
Trigo-Rocha et al., 2008	40	4.5	90%
Kim et al., 2008	124	6.8	82%

Three papers had reported QOL after implantation of AUS for PPI. At a mean of 39 months follow-up, Fleshner and Herschorn observed similar QOL in patients operated on with AUS as reported by patients without PPI [177]. Haab et al. found that after a mean follow-up of 7.2 years, 43 of 54 patients treated with an AUS reported good QOL [178]. Hussain et al. reported significant improvement of QOL in 34 men at a median of 24 months after AUS implantation [175]. However, in these studies, QOL was related to urological problems only, focusing on the patients' well-being related to urinary symptoms affecting daily activities, so-called incontinence-related or disease-specific QOL [179]. No studies regarding generic QOL after surgical treatment of PPI were identified.

A newly introduced AUS, the FlowSecure®, has a different design than the AMS800®, with an adjustable balloon capacity through a self-sealing port. Its effectiveness is not yet established. AUS implants with other designs are under ongoing development and evaluation [172].

Following recurrent incontinence after AUS implantation, there are several treatment options, depending on reason for failure. Incontinence can result from alteration in bladder function, atrophy of the urethra, mechanical failure of the device, or erosion/ infection [180]. Urethral atrophy may occur at the cuff site secondary to long-term mechanical compression. Treatment options consist of decreasing the cuff size, increasing the balloon pressure, implanting a double-cuff system, or proximal cuff repositioning. Regardless of the reason for mechanical failure, the relevant part of the AUS must be replaced. Erosion and/or infection are two major complications that almost always necessitate removal of the complete device [180].

1.4. Summary and reasons for doing this thesis

The high incidence of PCa and increasing use of RP as curative treatment leads to an increasing prevalence of PPI, in both younger middle-aged working men and older retired men. In Norway, patients have a basic right to have AEs evaluated and treated if indicated [181]. For a long time, PPI was neglected and represented a very little burden for the health care system in Norway. Information to patients and general practitioners about treatment of PPI was scarce and not highly prioritized by urologists. Until 2012, based on a national agreement, OUH Rikshospitalet was the only department in Norway offering surgical treatment of PPI, treating patients from the whole country. From the 1980's to 2006 there were between two and nine operations for PPI per year, with a 50-100% increase annually thereafter (18 in 2007, 74 in 2011), a trend similar to other countries [182]. Since 2012, a few more urological departments offer PPI surgery as the increasing demand was difficult to handle in one department only.

At that time (2007-2012) I worked as a resident in urology at Rikshospitalet and witnessed this development. I got to know these patients who were in despair because they were among "the unlucky 1%-2%" who experienced the PPI after RP. Their perception was very often that the prevalence of PPI should be very low.

I observed that there was a lack of research in Norway, and in Scandinavia in fact, regarding the true prevalence of PPI after RP, the pathophysiology and characteristics of severe PPI, as well as the outcome of PPI surgery, including QOL. Access to relevant local information is necessary to be able to give patients correct preoperative counselling, both before RP and before PPI surgery. "The satisfied patient is one whose outcomes match expectations" [147]. However, the problem is not present only in Norway as prevalence rates of PPI vary widely internationally, and others also report of patients' unrealistic expectations of continence, in spite of sober preoperative counselling [183].

The head of the Department of Urology at OUH Rikshospitalet, Professor Hans Hedlund, supported me when I announced my interest in doing research on PPI and its surgical treatment. As he was close to retirement, he arranged the contact with the National Advisory Unit on Late effects after Cancer Treatment, which became my workplace while doing this thesis. As a supervisor he also stimulated my work together with my two supervisors at the Unit, Professor Sophie D. Fosså, and Professor Alv A. Dahl.

2. THIS THESIS

2.1. Introduction

The work presented in this thesis began in 2010. At that time, increasing referral of patients with PPI to the Department of Urology at OUH Rikshospitalet was obvious with a considerable waiting list. The artificial urinary sphincter AMS800® was being increasingly used in these patients, and new surgical methods emerged, including the ProACT® and the AdVance® sling. However, none of these methods or their postoperative outcome had been evaluated at the Department.

At the same time two prospective studies of patients self-reporting AEs after curative treatment of PCa had been started at the Departments of Urology and Oncology at OUH Radiumhospitalet. Patients who had undergone RP there from 2005 to 2007 were included in a local study (the OUH study) and patients who had undergone RP at 14 of a total of 17 urological units in Norway in 2008 and 2009 were included in a national study (the NUCG VII study).

I was invited to take part in these studies to explore several aspects of PPI, such as identification of prevalence, predictors, urodynamic findings, and outcome of surgical treatment (Articles I and II). At the same time, at Rikshospitalet we started with a cross-sectional study of the outcome and QOL of the patients operated there for PPI between 2002 and 2010 (Article III).

Based on the Background and these opportunities at OUH, the current thesis was motivated by the following study aims:

2.2. Study aims

The current thesis comprises three sub-studies represented by Papers I-III.

Paper I: How should continence and incontinence after radical prostatectomy be evaluated? A prospective study of patient-ratings and changes over time

Background:
There is no international consensus on the optimal way to define, assess and grade PPI, which partially explains the wide range of prevalence rates reported, from 1% to 87%. Ellison et al. (2013) recently proposed a grading system for urinary incontinence based on the EPIC-26 into no/mild, moderate and severe incontinence.
Aims:
1) To examine how different definitions impact on the prevalence of patient-reported continence and incontinence at baseline and 12 months after RP, and analyzing changes.
2) To determine the descriptive validity of the PPI grading system proposed by Ellison et al.
3) To study baseline (pre- and peroperative) predictors of PPI at one year after RP.
Hypothesis:
Our hypothesis was that different methods of evaluating PPI would result in a wide difference of prevalence rates, and that the descriptive validity of the PPI grading system of Ellison et al. would be acceptable.

Paper II: Severe postprostatectomy incontinence: Is there a significant association between preoperative urodynamic findings and outcome of incontinence surgery?

Background:
There is little evidence for urodynamic investigation prior to surgical treatment of PPI, but it is recommended nevertheless. Bladder dysfunctions could theoretically compromise outcome of PPI surgery. We therefore wanted to study whether there were any associations between preoperative urodynamic findings and outcome of incontinence surgery in patients with severe PPI.

Aims:

1) To describe the results of the clinical urological examination of patients with severe PPI.

2) To collect patient-reported outcome of PPI surgery.

3) To study the associations between preoperative urodynamic findings and the outcome of PPI surgery.

Hypothesis:

Our hypothesis was that the presence of urodynamic bladder dysfunction preoperatively would predict an unsuccessful outcome after PPI surgery, defined as *dissatisfaction* or *use of more than one pad/day*.

Paper III: Study of generic quality of life in patients operated on for postprostatectomy incontinence.

Background:

Many patients complain of persistent PPI, which is associated with reduced quality of life (QOL). Reported postoperative continence rates after implantation of an artificial urinary sphincter (AUS) are high but the impact of this treatment on generic QOL is not well documented.

Aims:

1) To identify the rate of patients with poor generic QOL after implantation of an AUS for PPI (cases) and to compare this rate with that observed in men from the general population (controls).

2) To compare patients with poor generic QOL with those who report better QOL as to sociodemographic, cancer-related, surgical, urinary and sexual problems, mental distress, and patient satisfaction variables.

3) To identify the independent variables significantly associated with poor generic QOL.

Hypothesis:

Our hypothesis was that persistent urinary incontinence problems, rather than psychosocial variables, would be most strongly associated with poor generic QOL in such patients.

2.3. Patient sampling

Papers I and II (Figure 9)

The study sample for papers I and II derived from two prospective studies of AEs after RP for localized PCa, including 1) *the local 'OUH study'* of 156 patients treated between 2005 and 2007 [105], and 2) *the national 'NUCG VII study'* of 688 patients treated at a total of 14 urological units in Norway between 2008 and 2009 [184]. Both studies were initiated and analyzed at OUH.

Of the total of 844 included patients, 735 patients (87%) had completed all urinary incontinence items of the EPIC-50 or the UCLA-PCI, equivalent to the four items of the urinary incontinence domain (UID) of the EPIC-26, immediately before RP and 12 months postoperatively. Those patients were the basis for paper I.

In order to identify patients with persistent severe PPI in that sample, a new questionnaire (Q1) was sent out more than 12 months postoperatively (February 2011). The 94 patients who reported 'severe PPI' (defined below) were invited to a clinical examination and 76 patients (81%) attended. Fifty-three patients were subsequently referred for PPI surgery and by January 2014 46 patients had been operated with either an AUS or a sling. Two patients had died and were excluded from the second part of this study, leaving 44 patients evaluable postoperatively. They received a mailed follow-up questionnaire in January 2014 and 43 (98%) replied. The examined (N=76) and the operated patients (N=43) served as a basis for paper II (Figure 10).

Attrition analysis of the 109 patients who did not complete the baseline and 12-month questionnaires showed no significant differences from those who completed the questionnaires regarding baseline variables like sociodemographics, comorbidity, PCa stage and risk groups, and treatment approach and nerve sparing technique.

Attrition analysis of the 18 patients who declined clinical examination showed that they had higher mean UID score on the Q1 questionnaire (24 vs. 17, p=0.01) before PPI surgery, i.e. they had less PPI, when compared with those 76 patients who attended the clinical examination. Otherwise no significant differences were observed.

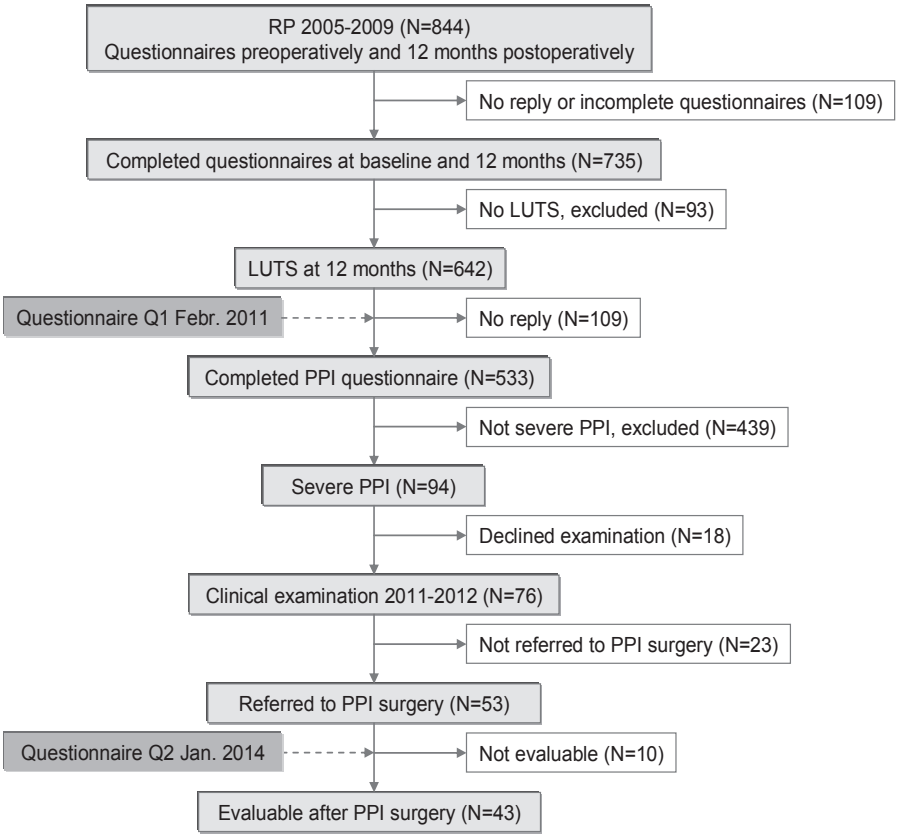


Figure 9. Patient flow diagram for papers I (first part of the diagram, N=735) and II (second part of the diagram, N=76)

Abbreviations: RP: Radical prostatectomy. LUTS: Lower urinary tract symptoms (including incontinence). PPI: Postprostatectomy incontinence. Questionnaire Q1: before PPI surgery, and Q2: after PPI surgery.

Paper III

Between January 2002 and June 2010, 107 patients had an AUS implanted for PPI at the Department of Urology, OUH Rikshospitalet. By January 2011, five patients had died and the AUS was removed in two patients. The remaining 100 patients were invited by mail to complete a follow-up questionnaire, and 85 complied.

Attrition analysis showed that the 15 non-responding patients did not differ significantly from the 85 complying patients regarding preoperative features like leakage and pad use, age and comorbidity at surgery, follow-up time or postoperative complications after PPI surgery.

Normative data and control group

For paper III a sample of men from the general population served as controls for the cases. The Survey of Living Conditions 2002 by Statistics Norway [185] included a questionnaire with the Short Form-36 QOL instrument to a representative sample of the Norwegian population aged 15 years and older (n = 6827, among which 3410 were males). The SF-36 was completed by 2514 males (76% response rate), among which 623 males were in the age range of our cases. We retrieved the shortened SF-12 QOL scorings of these men, and registered their level of education, paired relationship and work status. These data served as controls for the cases.

2.4. Methods

The methods behind this thesis are primarily based on questionnaires (Papers I-III) and secondarily based on the clinical evaluation of patients with severe PPI (Paper II).

Paper I was based on a prospective study of self-reported AEs after RP. The patients rated themselves at baseline (before RP) and at 12 months following RP, with either the UCLA-PCI or the EPIC-50. Paper II also reports a prospective study, a follow-up of the first study, where the patients received an additional questionnaire (Q1) more than 12 months after RP, to identify more definitely those with persistent severe PPI. These patients were then invited to a clinical examination including urodynamics, operated for PPI when indicated, and re-evaluated with questionnaire postoperatively (Q2). Paper III was a cross-sectional questionnaire-based study of self-reported outcome and QOL after PPI surgery.

PCa related variables (PSA at diagnosis, Gleason score of biopsies, clinical and pathological T stage, and positive surgical margins), surgery related variables (RP surgical approach [RRP vs. RARP], nerve sparing technique) (Paper I), preoperative features and postoperative events (Papers II and III) were retrieved from the Norwegian Prostate Cancer Registry and the patients' medical records, respectively. The risk group classification of D'Amico et al. was applied [43]. Current hormone therapy, previous pelvic radiotherapy, and relapse of PCa were self-reported.

The questionnaires, the clinical examination, the surgical methods, and statistical analyses are described below.

2.4.1. Questionnaires

Assessment of adverse effects: UCLA-PCI, EPIC-50 and EPIC-26

In this thesis, Norwegian versions of the UCLA-PCI, the EPIC-50 (Paper I) and the EPIC-26 questionnaires (Papers II, III) were used for rating AEs before and after RP.

The UCLA-PCI was specifically developed to assess typical AEs after treatment for PCa [82]. The EPIC-50 is a modified and extended version of the UCLA-PCI and includes additional items to capture concerns relevant to RP, RT, and androgen deprivation [95]. The EPIC-26 is an abbreviated version of the EPIC-50 [96].

The EPIC questionnaires cover the experience of urinary, sexual, bowel, and hormonal functions, and bother (problems) related to each function, and overall problems. Response options for each item form a 4- to 5-point Likert scale, and the scores are converted to a 0 – 100 scale with higher scores representing better function and less bother/problem [186]. Multi-item domain scores are the mean of the item scores of each domain (domain sum score divided on the number of items).

All three instruments have four identical items comprising *the urinary incontinence domain (UID)*. However, other items of the three instruments have been developed and changed over time; hence for example the items of the urinary obstructive/irritative domain (IRR) are not identical across instruments. The complete urinary domain of the most recent and recommended instrument, the EPIC-26, comprises nine items; the UID and the IRR with four items each, and one item addressing overall urinary problem (see Appendix).

Ellison et al. (2013) stratified PPI using the UID score of the EPIC-26, classifying a score of 0 – 49 as severe, 50 – 69 as moderate and 70 – 100 as mild/no PPI. This stratification was studied in our sample in Paper I [187]. For Paper II, severe PPI was defined as UID score <35 more than 12 months after RP (EPIC-26) corresponding to the 80th percentile of the UID scores on Q1, and those patients were invited to a clinical examination (Figure 9).

The sexual domain of the questionnaires was used in Papers I and III, but the hormonal and bowel domains were omitted from analysis (Paper III) or not used at all (Papers I and II) because of little relevance to RP patients.

Satisfaction with surgery

The patients' general satisfaction with surgery (both PCa and incontinence surgery) can be rated by one question on a 5-point Likert scale. Specific satisfaction with the outcome of

incontinence surgery was covered by five questions similar to those used by Litwiller et al. and Gousse et al. [188,189]. These questions were used in Papers II and III.

Other questionnaires: SF-12, HADS, EPQ, and WAI

There are some other psychosocial issues that are important to study in relation to AEs following PCa treatment, like generic QOL, anxiety, depression, basic personality traits (like neuroticism) and work ability. These topics were studied in Paper III.

Quality of life: SF-12

The SF-12 rates generic QOL and is an abridged version of the SF-36. The instrument consists of 12 items, with one or two items from each of eight health domains: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Responses are transformed into a 0-100 scale with higher score representing better QOL. Physical and mental QOL are expressed by the physical composite summary (PCS) and the mental composite summary (MCS) scores [102]. Based on T-transformation of the raw scores, the mean PCS and MCS scores in the Norwegian male population is 50 points and standard deviation 10 [190]. Mean scores above 50 represent better QOL and below 50 worse QOL compared to the general population [102].

The Hospital Anxiety and Depression Scale (HADS)

The HADS is commonly used to determine the levels of anxiety and depression that a person has experienced during the last week. The instrument consists of seven items on both the anxiety and the depression subscales. The subscale scores range from 0 (low) to 21 (high), with higher scores indicating more anxiety or depression [191]. Internal consistency in our sample was Cronbach's coefficient alpha 0.82 for depression and 0.83 for anxiety (Paper III).

Neuroticism: The Eysenck Personality Questionnaire (EPQ)

The EPQ short version assesses three basic personality traits including neuroticism. Neuroticism indicates the degree of nervousness and negative emotions from safe and positive to anxious and negative, which is important for the experience of disease and AEs [192-194]. An abridged version of the EPQ, with six items, is developed to assess

neuroticism only (EPQ-N) [195]. Each item is rated with yes (1) or no (0), giving a range from 0 (low) to 6 (high). Internal consistency in our sample was Cronbach's coefficient alpha 0.72 (Paper III).

The Work Ability Index (WAI)

The WAI is a validated instrument used in clinical occupational health and research to assess work ability during health examinations and workplace surveys [196,196,197]. There is one item rating current work ability (WA) that can be extracted from the WAI instrument and used on its own. Current WA compared with lifetime best is rated on an 11-point scale from 0 (completely unable to work) to 10 (WA at its best) and is also relevant for retired men.

Definitions of main outcomes

Continence categories

For Paper I, incontinence was reported according to several different definitions. Based on the EPIC-26 items *urinary control* and *use of pads* the sample was divided into three continence categories described by Herschorn et al. for ICS, including 1) total control and no pad use (perfect continence), 2) occasional dribbling without pad use and 3) daily pad use (the last category being inverted, defining incontinence instead of continence, to include all patients in either of the groups) [115].

In our study, preoperative continence was defined as abovementioned category 1 and incontinence included categories 2 and 3. Any category change from baseline to 12 months was defined as positive (better) or negative (worse). This categorization was compared with the continuous UID score. A UID score change of greater than ±10 on the scale of 0 to 100 scale was defined as a change (better/worse) [90,91].

In addition, Ellison et al.'s stratification of no/mild, moderate and severe PPI was studied when applied to our sample [187]. Category changes according to this stratification from baseline to 12 months were studied and compared to the abovementioned changes in categorical continence status. That comparison was done although we were aware that the two categorizations are not directly comparable since the latter lacks discrimination on the severe end.

Outcome after PPI surgery

In Paper II, successful outcome after PPI surgery (on the Q2 questionnaire) was defined in two ways: satisfaction with the operative result and use of ≤1 pad/day ('surgical success'). Satisfaction was dichotomized into 'very satisfied' or 'satisfied' ('satisfied patients') and 'uncertain' or 'dissatisfied' ('dissatisfied patients') with the PPI surgery. When comparing responses before surgery (Q1) with after surgery (Q2), *change* was defined as a difference on the response scale of at least one step for each item.

QOL as outcome

For Paper III, 'poor QOL' was defined as a score <40 on either PCS or MCS of the SF-12, and patients with higher scores belonged to the 'better QOL group'.

2.4.2. Clinical evaluation including urodynamics

Patients with severe PPI were evaluated with detailed history, physical examination, free uroflowmetry with measurement of post-void residual urine, invasive urodynamics and cystoscopy. Prior to their clinical visit they had performed three 24-hour pad tests and urinary diaries.

Number of pads and the amount of urinary leakage were noted based on the 24-hour pad tests. From the urinary diaries the micturition volumes (smallest, largest, mean, 24h-total) and frequency (number of micturitions per 24h) were recorded.

Prior to urodynamics, non-invasive catheter free uroflowmetry was performed and post-void residual urine was measured by catheterization. Bladder voiding efficiency (BVE) was calculated [156].

Urodynamic examination was conducted according to the standards of the ICS [158]. The standard multichannel cystometry was followed by pressure-flow study. A Ch 8 transurethral catheter measured vesical pressure and a rectal balloon catheter the total abdominal pressure, and subtracted detrusor pressure (Pdet) was calculated. Filling rate was 20 ml/min (within physiologic range).

Standard terminology regarding bladder and outlet dysfunction was applied [143,156,198]. *Detrusor overactivity* (DO) was defined as any involuntary detrusor contraction during the filling phase. *Bladder compliance* (C) > 20 ml/cmH_2O was considered normal, 10 – 20 impaired, and < 10 poor.

At capacity (the subjective feeling of a full bladder) the patient voluntarily voided and pressure-flow analysis was performed. Bladder outlet obstruction and bladder contractility were based on the ICS nomogram, and bladder outlet obstruction index (BOOI) and bladder contractility index (BCI), respectively.

For the purpose of Paper II some of the abovementioned indices were dichotomized, with normal cut-off values of BVE>80%, C>20 ml/cmH_2O and BCI≥100. BOOI <20 was considered unobstructed, 20-40 equivocal, and >20 obstructed [156]

Urodynamic stress incontinence is noted during filling cystometry and is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of DO (ICS definition) [143]. As urodynamic diagnosis of intrinsic sphincter deficiency (ISD) has a positive predictive value of 95% and a negative predictive value of 100% versus the complaint of stress urinary incontinence (SUI) on a clinical level [136], the latter was considered to be sufficient and used as a proxy for ISD.

Cystoscopy was performed with a rigid Ch 17.5 cystoscope with local gel anaesthesia and oral prophylactic antibiotics. The external urethral sphincter and bladder neck were inspected and any anatomical abnormality noted. All patients were asked to contract the sphincter voluntarily under visual inspection. The observations were classified as: obvious sphincter lesion, normal sphincter, bladder neck stenosis (surgery indicated, not passable for cystoscope Ch 17.5), and ability to contract sphincter (yes/no).

2.4.3. Surgical technique

PPI surgery was offered to patients with ISD and a significant amount of urinary leakage (>20 grams/24 hours) causing 'moderate or big problems' (item 4, Q1), regardless of urodynamic findings. Essentially, a sling was offered to patients with leakage <400 grams/24 hours, and an AUS to those with greater leakage volumes, also considering patients' preferences. Symptomatic detrusor overactivity (DO) and previous pelvic radiotherapy were relative contraindications to a sling. Bladder neck stenosis was treated before surgery for PPI was performed.

All patients had surgery under general anaesthesia and with broad-spectrum prophylactic antibiotics. For the AUS AMS800® the standard perineal approach was used to implant a single cuff around the bulbar urethra, and an abdominal incision for placement of

the pressure-regulating balloon and the pump [175]. Cuff size was usually 4.5 cm (range 4.0–5.5 cm), and the pressure-regulating balloon 61-70 cmH_2O.

The retrourethral transobturator slings AdVance® and A.M.I.®ATOMS were implanted through a perineal incision utilizing helical introducer needles [199,200]. The middle part of the AdVance® sling was fixed to the corpus spongiosum with four stitches of non-resorbable sutures. The port of the ATOMS® was filled peroperatively and additionally on postoperative follow-up visits if necessary

The AUS was activated 4 weeks postoperatively and the sling-patients had their first postoperative control with free uroflowmetry and post-void residual urine measurements six weeks after surgery. The patients had further follow-up according to individual needs. Postoperative events were retrieved from the patients' medical records.

2.4.4. Statistics

For all papers

Descriptive statistics included mean and standard deviation (SD) for continuous variables of normal distribution, median and range in case of skewed distributions, and proportions for categorical ones. Groups were compared with independent t-tests for continuous variables and with Fisher's exact tests for categorical variables. Nonparametric Mann-Whitney U tests were used in case of skewed distribution.

Internal consistencies of the domain items of the questionnaires were tested with the Cronbach's α coefficient, and all domains were within the accepted range of 0.65 to 0.90.

The level of significance was set at $p<0.05$ and all tests were two-sided. PASW Statistics 18.0 for PC (IBM Corporation, New York, USA) was used for statistical analyses.

Paper I

In Paper I, a clinically significant change was defined as a change of 10 points on the 0-100 scale of the UID score, which is commonly recommended [90,91]. Linear regression analyses were done to examine associations of baseline sociodemographic and cancer related independent variables and the degree of PPI (UID score) as the dependent variable. The variables that were significant in bivariate analysis were entered into the multivariable model, except age≥65 which was highly correlated to the continuous variable age. Additionally, the previously identified risk factors surgical approach, nerve sparing, and comorbidity were also

included, independently of their p-values. Collinearity statistics showed no collinearity between age, work status, comorbidity, sexual dysfunction, and incontinence (both the variance inflation factors and the tolerance statistics were close to 1 for each of the variables, i.e. no multicollinearity).

Strengths of association were expressed as B and standardized β coefficients. As a decreasing value of the dependent variable (UID score 0-100) reflects increasing degree of PPI a positive β coefficient represents a positive association and a negative β represents an inverse association with increasing degree of PPI.

Paper II

In Paper II, the two methods of outcome evaluation (satisfaction and using ≤1 pad/day) were compared using Cohen's kappa coefficient of agreement showing a value of κ 0.25, meaning a low degree of overlap (i.e. they were statistically independent). The κ coefficient compensates for agreement by chance.

Paper III

In Paper III, statistically significant group differences were examined for clinical significance using effect sizes. For continuous variables, we used Cohen's coefficient d; and for 2x2 contingency tables, the differences between arcsine transformed proportions. Effect size values ≥0.40 were considered as clinically significant based on the recommendations of Cohen and Sloan et al. [93,94].

The associations between independent variables and poor QOL as dependent variable were analyzed with bivariate and multivariable logistic regression analyses. The strengths of association were expressed as odds ratios (ORs), and 95% confidence intervals (CI) were given as appropriate. The explanatory power of each model was given as Nagelkerke's R^2.

2.4.5. Ethics

The Regional Committee for Medicine and Health Research Ethics of South-East Norway and the institutional review board at OUH approved the studies of this thesis. All patients returning questionnaires gave written, informed consent.

2.5. Design considerations and possible errors

The study designs of Papers I and II were prospective follow-up studies, while the study design of Paper III was cross-sectional. The cross-sectional design and the lack of a sham-operated control group in the study of Paper III preclude any conclusions regarding causality of the associations with poor QOL in patients operated with an AUS.

Measurement error in clinical studies can be divided into random and systematic errors. *Random errors* are due to random fluctuations (or chance) in the data collected. The effects of random error are predictable; it causes larger variance, i.e. less precise estimates, which in general leads to underestimates of relative risks.

Systematic errors (or bias) lead to erroneous associations between exposure and disease expression. The effects of systematic error are not predictable and can lead to over- or under-estimated effects. Examples of systematic errors are *selection bias*, *information bias*, and *confounding* [201,202].

Selection bias occurs when the criteria for selecting subjects into a study differ between 'index' and 'comparison' subjects, i.e. the selected participants are different from non-participants or cases are different from controls. In all of our samples the patients were consecutively enrolled, and that method precluded selection bias. We also made attrition analyses in all three papers, documenting that the participants and non-participants did not differ significantly on key variables.

In *information bias* the nature or quality of measurement differs between 'index' and 'comparison' subjects (misclassification of exposure and/or disease). Non-differential misclassification (same for both 'index' and 'comparison' subjects) leads to more serious error, i.e. bias, than differential misclassification. Based on questionnaire responses we have classified the patients in paper I and II concerning their urinary leakage. The variation in the patients' rating of themselves in this regard represents random error rather than information bias.

Confounding is the distortion or mixing of effects between an exposure, an outcome, and a third variable known as a confounder. Confounding leads to a distorted association between the exposure and the outcome. We therefore adjusted for available key variables, like sociodemographics, PCa stage and surgical approach, when analyzing for significant associations to avoid the problem of confounding as much as possible. Some confounders,

like body mass index (BMI) and serum testosterone level [203], were impossible to adjust for in our studies, however, and they may represent a source of error not identifiable in our studies.

These types of bias can be avoided by randomization of patients; otherwise attrition analyses of the non-participants' known variables represent a helpful control. Attrition analyses in all three sub-studies in this thesis showed that there were no significant differences between participants and non-participants on key variables. The only exception was in study II, where the participants had higher mean UID score than non-participants, i.e. the participants were more representative for our objective to perform urodynamics in patients with severe PPI.

In order to evaluate generalizability of the prospective studies of AEs after RP (Papers I and II), an attrition analysis was originally done for a substudy of the NUCG VII study [184]. The attrition analysis compared some of the patients included in NUCG VII study (N=521) with a control group (N=591) of non-included patients who underwent RP during the study period, regarding age, RRP vs. RARP, pT category and RP specimen Gleason score (data provided by the Norwegian Prostate Cancer Registry). There was a significantly higher proportion of RARP in the study sample compared to the control group, otherwise no other significant differences were found. This analysis confirmed the generalizability to the rest of Norwegian urological departments. External validity outside of Norwegian health care is discussed below.

In statistical analysis, there are two additional errors important to be aware of; type I and type II statistical errors [204]. In an ideal world we would always reject the null hypothesis when it is false, and we would not reject the null hypothesis when it is true. *Type I error* involves rejection of a null hypothesis that is actually true, which is equivalent to false positives. Alpha (α) indicates the maximum probability that we have a type I error, for example 5% when α is 0.05 (significance level). This means that there is a 5% probability that we will reject a true null hypothesis.

Type II error occurs when we do not reject a null hypothesis that is false, which is equivalent to false negatives. The probability of a type II error is given by the letter beta (β), which is related to the power or sensitivity of the study, denoted by $1 - \beta$. In studies with small samples there is a higher risk of type II errors than in studies with larger samples. There was a considerable risk of type II error in both Papers II and III due to small sample size, i.e.

that we missed significant associations due to low statistical power. Therefore, the results of these studies should be verified by studies with larger samples.

There are a few other terms and concepts that are relevant when dealing with *patient-reported outcome measures* (PROM), including validity, reliability, and responsiveness, also known as psychometric properties of an instrument. The questionnaires used in this thesis are internationally validated and recommended when studying AEs after RP (the UCLA-PCI, the EPIC-50, the EPIC-26, and the SF-12) [97,99].

Validity refers to "the degree to which an instrument measures the construct(s) it purports to measure" [205]. Validity contains the following concepts: face validity/descriptive validity (the instrument obviously seems to measure what it claims), content validity (the instrument measures what it claims to measure), construct validity (correlation with other instruments measuring the same construct), criterion validity (adequate reflection of a "gold standard"), and predictive validity (the instrument is able to predict the outcomes, like AEs). The instruments used in papers I-III fulfilled most of these types of validity.

In the medical literature we also find the terms *internal validity* (if sound conclusions based on the study is warranted) and *external validity* (generalizability of the findings to other samples or situations), referring to study design rather than to the instruments used. Both are of course of great importance when discussing results of a study. In the three sub-studies we make no assumptions of cause and effect, we only report on associations and predictive variables. However, external validity is discussed in Paper I.

Our results (Paper I) were obtained in a health care system without population-based PSA screening, in which more than half of the patients were operated on by high volume surgeons (greater than 50 RP's per year) and more than two-thirds underwent RARP, which is similar to the current practice in many other countries in Europe and in North America. Therefore, we consider that our results can be generalized beyond Norway and have some external validity. The prevalence of PPI and associated risk factors that we found may well be relevant to other samples in Europe and in North America.

Reliability refers to the consistency and reproducibility of an instrument [205]. The concept reliability contains *internal consistency* (interrelatedness among the items), *reliability* (variance reflecting true differences), *test-retest reliability* (variance over time), and *measurement error* (error not caused by true changes). For example, the internal consistency of items within a domain can be tested with Cronbach's α coefficient. It should be in the

range of 0.65-0.90, as higher values indicate unnecessary overlap [201,206]. The internal consistency of each domain of the relevant instruments used in this thesis (the EPIC, the HADS, and the EPQ) was calculated for our samples and all were found to be satisfactory.

Responsiveness (sensitivity to change) refers to the ability of an instrument to detect change over time in the construct to be measured [205].

Response shift is not a property of the instrument but rather a phenomenon that may occur to individuals over time during a study. It refers to an adaptation of the response resulting from changes in an individual's internal standards, values, or conceptualization of AEs/QOL and can affect the reliability and validity of the instrument in use [87,207,208]. Response shift may arise from a change in the individual's health over time and leads to a change in how that individual views their AEs and QOL, i.e. getting used to a certain dysfunction. This may in turn lead to ambiguous or paradoxical findings and can be hard to correct for but is important to be aware of when analyzing changes in QOL over time. This phenomenon may be relevant for patients with PPI, both when reporting urinary AEs after RP as time goes by, and when reporting outcome and QOL after surgical treatment of PPI. Both of which can be related to preoperative expectations. Response shift is difficult to estimate, and the suggested methods are not generally accepted [208]. Therefore we did not do any such calculations. However, it is especially important to bear in mind when analyzing the results of Papers II and III of this thesis.

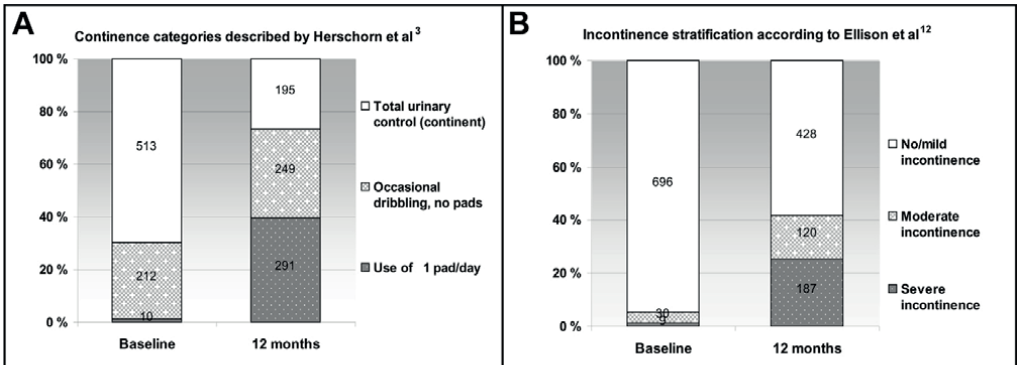
2.6. Main findings

Paper I

The aims of this study were to evaluate the prevalence of patient-reported continence and incontinence before and 12 months after RP applying different definitions, as well as analyzing the changes, determine the descriptive validity of the PPI stratification proposed by Ellison et al., and to study baseline predictors of persistent PPI.

1) Prevalence, incontinence degree and changes (Figure 10, Table 5)

At baseline 513 patients (70%) reported total urinary control (perfect continence), 212 patients (29%) had occasional dribbling without pad use and 10 patients (1%) used pads daily. Based on the stratification of Ellison et al. 696 patients (95%) had no/mild, 30 (4%) had moderate and 9 (1%) had severe incontinence at baseline.



Baseline: N (%)	12 months: Total control	Dribbling, no pads	≥1 pad/day	Total
Total urinary control	166 (32)	162 (32)	185 (36)	513 (100)
Dribbling, no pads	28 (13)	84 (40)	100 (47)	212 (100)
Use of ≥1 pad/day	1 (10)	3 (30)	6 (60)	10 (100)
Total	195 (27)	249 (34)	291 (40)	735 (100)

Baseline: N (%)	12 months: No/mild incontinence	Moderate incontinence	Severe incontinence	Total
No/mild incontinence	415 (60)	113 (16)	168 (24)	696 (100)
Moderate incontinence	10 (33)	7 (23)	13 (43)	30 (100)
Severe incontinence	3 (33)	0 (0)	6 (67)	9 (100)
Total	428 (58)	120 (16)	187 (25)	735 (100)

Figure 10. Prevalence of continence and incontinence before and after RP

A, continence categories described by Herschorn et al. based on two of the UID items 'urinary control' and 'pad use'. B, incontinence stratification based on Ellison et al. Green areas indicate improved continence. Red areas indicate worse continence. Blue areas indicate stable or little change. Hatched area indicates stable or worse (more pads used).

At 12-month follow-up 195 patients (26%) reported total urinary control, 249 (34%) had occasional dribbling without pad use and 291 (40%) used pads daily. According to Ellison et al. 428 patients (58%) had no/mild, 120 (16%) had moderate and 187 (25%) had severe PPI at 12 months.

Figure 10 and Table 5 show changes from baseline to 12 months. When the 513 patients (70%) with total urinary control preoperatively were classified according to Herschorn et al. at the 12-month follow-up, 32% still had total urinary control, 32% had occasional dribbling and 36% used pads (Figure 10). Of the 222 patients (30%) with incontinence preoperatively 14% reported better continence, 41% were stable and 45% had worse incontinence at follow-up. The relative risk was 1.29, i.e. the risk of PPI was 29% higher in patients who were preoperatively incontinent vs. continent.

Comparing changes in continence status according to the three continence categories or change in continuous UID score revealed moderate agreement (k=0.69). Comparing changes according to the continence categories described by Herschorn et al. and the PPI stratification by Ellison et al. showed less agreement (k=0.47). According to Ellison et al. a larger proportion of patients were defined as stable compared to the two other methods (58% vs. 35% to 38%, p <0.001, Table 5).

Table 5. Continence status change from baseline to 12 months after RP

UID continence category change [a]	Improved N (%)	Stable N (%)	Worse N (%)	Total N (%)
Continuous score [b]				
Improved	**14 (44)**	18 (56)	0	32 (100)
Stable	12 (5)	**208 (81)**	36 (14)	256 (100)
Worse	0	51 (11)	**396 (89)**	447 (100)
Stratification [c]				
Improved	**7 (22)**	25 (78)	0	32 (100)
Stable	6 (2)	**234 (91)**	16 (6)	256 (100)
Worse	0	169 (38)	**278 (62)**	447 (100)

[a] UID= Urinary Incontience Domain. Based on pad use and urinary control (total control, leakage but no pads or pads according to Herschorn et al. [b] Change of 10 or more points on 0 to 100 scale from baseline to 12 months after RP was defined as change (k= 0.69). [c] According to Ellison et al11 (k= 0.47).

2) Descriptive validity of the stratification of PPI by Ellison et al. (Table 6)

According to the stratification proposed by Ellison et al., the prevalence of severe PPI was 25% (95% CI 22%-29%) in our sample 12 months after RP. However, when severe PPI was defined as total incontinence, 3% of patients reported 'no urinary control' at 12 months, including 1% of those younger than 65 years and 6% of men 65 years old or older ($p < 0.001$).

Table 6. Responses to the urinary incontinence domain (UID) before (baseline) and 12 months after radical prostatectomy (Paper I)

Question: How often have you leaked urine the past for weeks?		
Response item	**Baseline, N (%)**	**12 months, N (%)**
More than once a day	20 (2.7)	324 (44.1)
About once a day	21 (2.8)	56 (7.6)
More than once a week	9 (1.2)	54 (7.3)
About once a week	35 (4.7)	97 (13.2)
Rarely or never	650 (88.4)	204 (27.8)
Question: Which of the following best describes your urinary control?		
Response item	**Baseline, N (%)**	**12 months, N (%)**
Total control	514 (69.9)	195 (26.5)
Occasional dribbling	1 (0.1)	480 (65.3)
Frequent dribbling	215 (29.3)	39 (5.3)
No control	5 (0.7)	21 (2.9)
Question: How many pads did you use per day to control urinary leakage?		
Response item	**Baseline, N (%)**	**12 months, N (%)**
None	725 (98.6)	444 (60.4)
1 pad per day	7 (1.0)	139 (18.9)
2 pads per day	2 (0.3)	98 (13.3)
3 or more pads per day	1 (0.1)	54 (7.3)
Question: How big a problem, if any, has dripping or leaking urine been for you?		
Response item	**Baseline, N (%)**	**12 months, N (%)**
No problem	605 (82.3)	315 (42.9)
Very small problem	100 (13.6)	194 (26.4)
Small problem	16 (2.2)	94 (12.8)
Moderate problem	13 (1.8)	84 (11.4)
Big problem	1 (0.1)	48 (6.5)

3) Baseline predictors of PPI at 12 months (Table 7)

On bivariate analysis the preoperative variables age 65 years or greater, not working, sexual dysfunction and incontinence were significantly associated with PPI at 12 months. No significant association was observed in D'Amico risk group, surgical methods, nerve sparing technique or pathological T stage. On multivariable analysis only preoperative urinary incontinence and sexual dysfunction remained significant predictors of persistent PPI 12 months after RP.

Table 7. Linear regression analysis of baseline and cancer related variables associated with PPI at 12-month follow-up in 735 patients based on continuous UID score

	Bivariate analysis			Multivariable analysis [a]		
Variables	**B**	**β**	**p-value**	**B**	**β**	**p-value**
Baseline						
Continent [b]	-10.0	-0.17	**<0.001**	-6.11	-0.16	**<0.001**
Age	0.73	0.14	**<0.001**	-0.12	-0.02	0.70
Currently working	-8.31	-0.15	**<0.001**	-3.57	-0.06	0.20
Comorbidity present	3.90	0.07	0.07	-2.78	-0.05	0.20
Sexual dysfunction [c]	0.23	0.21	**<0.001**	0.21	0.19	**<0.001**
Clinical T stage:						
≤T2a	1.00			1.00		
T2b-T2c	4.17	0.05	0.15	3.52	0.05	0.25
≥T3	8.23	0.07	0.08	9.42	0.08	0.05
Surgical approach:						
RARP	1.00			1.00		
RRP	3.35	0.06	0.14	3.71	0.06	0.11
Nerve sparing [d]	-3.01	-0.05	0.14	-1.79	-0.03	0.41

[a] All variables significant on bivariate analysis were entered in multivariable analysis except age ≥65 years, in addition to some controversial variables of special interest. Variables not entered in multivariable analysis are not shown in this table. [b] Based on patient reported total urinary control at baseline vs not. [c] Based on continuous sexual domain score 0 to 100 at baseline. [d] Based on surgeon reported unilateral and bilateral technique.

Paper II

The aims of this study were: 1) to describe the results of the clinical examination of patients with severe PPI, 2) to collect patient-reported outcome of PPI surgery, and 3) to study the associations between 1) and 2).

1) Clinical findings

The 76 participating patients used 1-13 pads/24 hours and leaked 4-1870g/24 hours. All patients but one complained of SUI (thus being categorized as having ISD) and 12 complained of urgency urinary incontinence (UUI). On free uroflowmetry and post-void residual measurement, three patients had reduced bladder voiding efficiency (BVE 46%-68%), neither of whom had a stenosis but weak bladder contractility (low bladder contractility index, BCI). On invasive urodynamics 52 patients (68%) had bladder dysfunction. Altogether, ISD was coexisting with one or more bladder dysfunctions in 51 patients (67%) and ISD was the only dysfunction in 24 patients (32%).

2) Outcome of PPI surgery

Successful outcome of PPI surgery was defined in two ways: *Satisfaction* and *use of ≤1 pad/day ('success')*. Thirty-two patients (74%) were satisfied (17 'very satisfied', 15 'satisfied') and eleven (26%) were dissatisfied (8 'uncertain', 3 'dissatisfied') with the outcome of surgery. Fifteen patients did no longer use pads, 18 used 1 pad/day (thus 33 (77%) in the 'success' group), five used 2 pads/day, and five used ≥3 pads/day.

3) Associations between clinical findings and outcome of PPI surgery

Preoperative urodynamic bladder dysfunction and amount of leakage (g/24h) were not significantly associated with either method of evaluating surgical outcome (satisfaction and pad use).

Using fewer pads preoperatively, a higher preoperative mean UID score, and a longer PPI interval (time from RP to PPI surgery) were positively associated with the outcome measure *success (using ≤1 pad)*. A longer PPI interval was the only preoperative variable positively associated with *satisfaction*.

Finally, patients with presence of urodynamic bladder dysfunction preoperatively were compared to those without. No significant differences were observed regarding

preoperative amount of leakage, pad use, or mean UID score, postoperative UID and IRR scores, or outcome of PPI surgery.

Paper III

The aims of this study were study the prevalence of poor generic QOL in patients who had an AUS implanted for PPI, comparing with controls, and to identify variables associated with poor generic QOL, by comparing with those reporting better QOL.

1) Prevalence of poor QOL

At a median of 26 months after implantation of an AUS, 30 of the 85 patients, i.e. 35% (95% CI 25–45%) of the cases showed poor QOL compared with 27% (95% CI 24–31%) of the controls (P = 0.97 adjusted for age and work status).

2) QOL group comparisons

Comparing the poor and the better QOL groups, no significant differences were observed regarding preoperative features like urodynamic abnormalities and pad weight/24h. In bivariate analyses, urinary and sexual problems were significantly more common in the poor QOL group compared with the better QOL group. The presence of somatic comorbidity, reduced work ability, surgical revision of the AUS, anxiety and depression were significantly associated with poor generic QOL.

3) Independent variables significantly associated with poor generic QOL

In multivariable analysis, only reduced work ability and increased level of depression remained strongly associated with poor QOL. Our hypothesis of the strong influence of urinary incontinence problems on generic QOL was not supported in the study.

2.7. Discussion

Paper I

Aim 1

Perfect continence (total urinary control) was reported by 70% at baseline and by 26% 12 months after RP. However, if we include those with occasional leakage but no pad use, which is commonly done [144,146], 'continence rates' would be 99% and 60% at baseline and 12 months, respectively. Thus, the definition applied plays a major role in reported prevalence rates. Preoperative continence rates are rarely reported in the literature. The 'perfect continence rate' 12 months after RP has been reported to be 33% to 87% and the 'continence rate' (i.e. no pad use) 65% to 98%, somewhat higher than we observed [114,144,146].

When defined as any pad use or any leakage, previously reported PPI rates are 2% to 35% and 11% to 72%, respectively (Table 8) [114,146]. In contrast, as many as 40% of our patients used pads daily and 74% reported any degree of leakage 12 months postoperatively. The reason for this high prevalence may have been older age and more advanced PCa in our sample, as well as cultural differences with lower thresholds for reporting urinary leakage and pad use [209].

Table 8. Definitions of incontinence 12 months after radical prostatectomy

Definition	Reported rates	Current study
Any leakage	11% - 72% [114,144,146]	74%
Any use of pads	2% - 35% [114,144,146]	40%
Frequent leakage/no control	10% [a] [210]	8%
Total incontinence	5% - 10% [150]	3%
EPIC UID score 0-49 [b]	6% [211]	25%
Require surgery	5% - 9% [114,115]	7%
Moderate/severe bother	22% [212]	18%

[a] Reported rate at 24 months after RP. [b] EPIC-26 Urinary Incontinence Domain (scale 0-100).

Irritative/obstructive symptoms, i.e. symptoms indicative of bladder dysfunction or obstruction (prostate enlargement preoperatively, anastomosis stenosis postoperatively), usually improve after RP [112,122;138,213]. On the other hand, the prevalence of irritative/obstructive symptoms are progressively increasing over time in men in the general population, patients with PCa under WW, and patients with PCa treated with RT. This difference (RP vs. general population, WW, RT) suggests that the prostate is the primary contributor to these symptoms in men and that RP has a therapeutic benefit, at least in patients with these symptoms before RP [122,213]. However, men with little or no irritative/obstructive symptoms before RP may experience an increase in such symptoms following RP due to de novo bladder dysfunctions or obstruction [122,213].

These preoperative symptoms of urgency incontinence, postmicturition dribble and overflow incontinence may thus improve with de-obstruction after RP while preoperative stress urinary incontinence does not improve [144,214]. Many PPI studies only included continent patients at baseline and changes in continence status are regularly presumed to be from better to worse, i.e. from continence to incontinence [146]. However, we included patients who were incontinent at baseline and found that 14% of them improved at follow-up, probably due to relief of obstruction and improvement of urgency incontinence, postmicturition dribble and overflow incontinence.

Aim 2

Validated symptom scales with several items of more or less objective (pad use) and subjective (bother) experience, like the EPIC-26, may be useful when grading PPI, as several different aspects of urinary leakage are considered [82,149,187,215,215]. However, there is not yet international consensus regarding stratification or grading of urinary incontinence into mild, moderate and severe forms.

Some authors have proposed ‘severe incontinence’ to be ‘total incontinence’ while Ellison et al. recently proposed a score of 0-49 on the 0-100 scale of the EPIC-26 UID for ‘severe incontinence’, which includes a lot more patients than those reporting ‘total incontinence’[150,187]. In our opinion, the cut-off that Ellison et al. used for severe PPI seems unreasonably lenient since it leads to inclusion of a considerable proportion of patients with moderate PPI in the severe PPI group. For example, a patient reporting the combination of occasional dribbling (score 67), leaking once daily (score 25), using one pad (score 67) and

considering it a moderate problem (score 25) would have a mean UID score of 46, and thus being a case with severe PPI according to Ellison et al.

In our sample at follow-up the prevalence of severe PPI according to Ellison et al. was 25% (95% CI 22%-29%), which is quite high, particularly compared to the 6% that Ellison et al. reported in their sample [211]. However, when severe PPI was defined as 'total incontinence', previously reported rates were 5% to 10%, increasing with age [150]. These values are in better agreement with our finding that 3% of patients reported no urinary control at 12 months, including 1% of those younger than 65 years and 6% of patients 65 years or older ($p < 0.001$).

Therefore, our findings do not support the descriptive validity of the severe PPI definition of Ellison et al. and our hypothesis was not supported.

On the other end of the scale (no/mild incontinence), Krupski et al. found that of patients reporting a score of 80-100 on the 0-100 scale of the UCLA-PCI, 99% used no pads, 71% reported total control, and 65% reported not leaking urine at all [4], indicating that these different aspects of urinary incontinence do not always correlate perfectly.

Nonetheless, subjective bother (problem with urinary leakage) should probably be included in a PPI severity grading since this aspect of urinary leakage decreases QOL and drives treatment [212]. However, the cut-offs for such a grading remain to be identified.

Should bother or pad use be weighted more when defining PPI severity? It is important to distinguish between patients who leak enough to require pads and those who do not since pad use significantly affects QOL [4,212,216]. However, in our study patients with all degrees of PPI, including those not using pads, reported a 'moderate/big problem with leakage'. For an international consensus the PPI severity grading should be meaningful and useful, and not only easy to apply, such as 'pad use'. The scores on the 0-100 scale of the EPIC-26 UID do probably not mean much to the individual patient though, and may therefore seem quite meaningless during preoperative counselling. These scores may rather be useful when reporting AEs and QOL outcomes after RP.

Aim 3

Older age and preoperative urinary incontinence can be considered established predictors of PPI, as identified by previous studies [144,217]. Nevertheless, several of our patients with preoperative incontinence reported improvement, probably related to relief of obstruction. Older age was no longer significant when adjusting for preoperative sexual dysfunction and urinary incontinence, which emerged as more important.

Preoperative sexual dysfunction was the strongest predictor of PPI in this study. Preoperative erectile dysfunction is a predictor of PPI with the hypothesis that erectile dysfunction might be a marker of pelvic vascular disease that eventually affects the function of the external urinary sphincter [218,218,219].

Surprisingly, unemployment (not working) preoperatively was associated with PPI, also when adjusted for age. To our knowledge this is a new finding. Employment may represent health and stamina beyond age and comorbidity, and may thereby explain the negative association with PPI. Unemployment was a stronger predictor than older age. However, neither was significant in the multivariable analysis where only preoperative incontinence and sexual dysfunction remained significant.

There are conflicting findings in the literature on the effect of PCa stage, surgical approach and nerve sparing on PPI, but most large series show no significant associations, corresponding to our findings [115,217].

We could not adjust for some previously identified risk factors of PPI, including metabolic factors such as waist circumference, body mass index, testosterone level and annual surgeon RP volume. A previous study of a subsample of our patients showed no significant association between surgeon volume and PPI, but RP at university hospitals was more favourable than at community hospitals [184].

Strengths and limitations

We used well-established questionnaires and had a large sample size and high response rates to the questionnaires. Participants did not differ from non-participants so that they may be considered representative of the 844 patients primarily included in the study.

Our results were obtained in a health care system without population-based PSA screening, in which more than half of the patients were operated on by high volume surgeons (greater than 50 RP/year) and more than two-thirds underwent RARP. This practice is similar

to that of many other countries in Europe and in North America. Therefore, we consider that our results in this study can be generalized beyond Norway.

The missing discrimination of the type of urinary incontinence is a limitation. The 12-month follow-up could be considered too short for a study of persistent PPI, although little improvement is expected after that time. The major limitation in reporting PPI prevalence is the lack of international consensus on the optimal way to define, assess and grade PPI.

Paper II

Aim 1

Concerning urodynamic findings after RP, the Committee on Surgical Treatment of Urinary Incontinence in Men (2010 and 2013) stated that ISD was the sole finding in more than two-thirds of patients with PPI, and that a combination of sphincter and bladder dysfunction was less common [115,144,144]. Porena et al. (2007) found in their review that previous reports varied widely concerning bladder dysfunction following RP [137]. The studies referred to in these reviews had very different follow-up and timing of urodynamic evaluation following RP, though, which may have contributed to the different findings.

Kadono et al. recently published their results comparing urodynamics in 87 patients before and 9-11 days after RARP [220]. Bladder dysfunctions were present both preoperatively and postoperatively, with significant changes in some parameters (bladder capacity, bladder compliance), while the proportion of patients with DO did not increase significantly (25% to 29%, p=0.44). ISD was found in none preoperatively and in 86% postoperatively.

We found urodynamic abnormalities coexisting with ISD in two-thirds of our patients with persistent severe PPI more than one year after RP. Among the 76 patients with self-reported persistent severe PPI 99% had intrinsic sphincter deficiency (ISD), in 67% coexisting with urodynamic bladder dysfunction, DO in 29%. Although not directly comparable, due to different length of follow-up and patient sampling method, our results are quite similar to the abovementioned after RP.

However, some findings on invasive urodynamics were contradictory to findings on free uroflowmetry with post-void residual urine measurement and urethrocystoscopy in our patients. The bladder contractility and the bladder outlet can usually be assessed by a pressure-flow study, but standard urodynamic definitions may be invalid in prostatectomized men [161,221], which could explain these contradictons: According to Schäfer's nomogram and

the bladder contractility index (BCI) 38 of our patients were defined as having weak bladder contractility (low BCI). However, low BCI was confirmed as clinically relevant only in the three patients with reduced bladder voiding efficiency (BVE <80%), i.e. those with significant post-void residual urine, and this finding is in accordance with previous studies [137,222,222]. Similarly, 23 patients were regarded as 'obstructed' or 'equivocal' according to the bladder outlet obstruction index (BOOI); but 19 had normal free flow and/or no stenosis. Valsalva voiding was not significantly more common in patients with high BOOI or low BCI.

Elliott and Comiter (2012) questioned the use of the BCI in prostatectomized men since it was not originally intended for use in that context, but rather in patients with prostatic obstruction [223]. After RP the urethra offers little resistance to micturition, thus low detrusor pressures are sufficient for a normal urinary flow rate [161]. Hence, the false positive rate of weak contractility (i.e. BCI <100) may be high in prostatectomized patients as the Pdet@Qmax can be very low in these patients.

Instead, Elliott and Comiter suggested the use of maximum isometric pressure (Piso) during mid-void while occluding the penile urethra (mechanical stop test). When using a Piso <50cmH_2O as a cut-off for detrusor underactivity the proportion of men with PPI diagnosed with weak contractility was reduced to 40% compared with 68% when using the BCI. Of those with detrusor underactivity using the BCI criteria, 57% had a Piso value suggesting normal strength [223]. The Piso method could give more correct results in prostatectomized men, but larger studies are needed to verify that.

Other proposed definitions of detrusor underactivity after RP are Qmax <12 ml/sec and Pdet@Qmax <30 cmH_2O [161], Qmax <15 ml/sec and Pdet@Qmax <25 cmH_2O [224], and Qmax <15 ml/sec and Pdet@Qmax <20 cmH_2O [225]. A recent review regarding detrusor underactivity (of any etiology), confirms the confusion around the methods of evaluating detrusor contractility and states that there is a need to reach a consensus [221].

Hence, the indices BOOI and BCI can be misleading in patients with PPI, and should be interpreted with care and rather be used in addition to free uroflowmetry with post-void residual measurement and urethrocystoscopy.

Thus, when excluding those with only high BOOI and/or low BCI in our sample, the proportion of patients with bladder dysfunctions coexisting with ISD was reduced from 67% to 38%. Nevertheless, bladder dysfunction, with or without this exclusion, was not

significantly associated with the amount of urinary leakage (g/24h) or mean UID score prior to PPI surgery, being referred to surgery, or the outcome of surgery. It should be emphasized however, that all the patients with symptomatic DO (i.e. UUI) preoperatively had an AUS implanted, not a sling.

Aim 2

Of the 43 operated patients, *satisfaction* was reported by 74% and *using ≤1 pad/day* by 77%. These results are comparable to previously published reports of outcome after surgery with an AUS or a sling for PPI [144].

Aim 3

Urodynamic investigation is recommended in the evaluation of PPI, especially prior to surgical treatment, by the Fourth International Consultation on Incontinence, the European Association of Urology guidelines, and the American Urological Association guidelines [67,115,162-164]. The recommendation of urodynamic investigation before surgical treatment of PPI is not evidence-based, however [165,166].

Most patients tolerate invasive urodynamics well, but in a recent study by Suskind et al., 38% of the patients reported physical or emotional discomfort, with placement of the urethral catheter causing the most physical discomfort (Suskind et al. 2014a). There is also a risk of AEs after urodynamics, especially urinary tract infections, although rare [226]. Hence, unnecessary invasive diagnostic procedures should be avoided. Urodynamics should only be performed when there is a question that can be answered and that answer would affect treatment choice or outcome [227].

The 2014 EAU Guidelines on Urinary Incontinence state that no studies have examined the clinical usefulness of urodynamics in patients with PPI, and that the ability of urodynamics to predict surgical outcome for PPI is inconsistent [172]. It has been shown that preoperative urodynamic abnormalities have no adverse effect on the outcome of PPI surgery, which is in agreement with the findings in our study [168,169,228-230]. The presence of bladder dysfunction preoperatively was not predictive of the outcome of PPI surgery in our study; hence our hypothesis was not supported.

In a recent review by Jura and Comiter (2014), the role of urodynamics in patients with PPI is comprehensively discussed [227]. The available evidence indicates that the non-

compressive sling (AdVance®) and the AUS (AMS800®) are not contraindicated in case of detrusor underactivity or overactivity, while the compressive slings (InVance®, TOMS®, Argus®) should probably be avoided in such cases. They suggest that urodynamics are unnecessary if the AUS is the treatment of choice, based on amount of leakage, prior RT, patient preference, or previous sling/AUS implantation. They pointed out that DO or impaired compliance (in nonradiated patients) typically resolves after PPI surgery as the normal cycle of adequate filling and emptying is re-established [227]. Their review and conclusions are in accordance with our findings.

A longer PPI interval was the only preoperative variable associated with both methods of evaluating successful outcome in our study. This observation has not been reported previously and is difficult to explain. It could be related to a response shift in the patients, i.e. getting used to PPI with time and having lower expectations for PPI surgery [207].

These results rather indicate that invasive urodynamic examinations may be somewhat restricted, and not performed in all patients before PPI surgery. Major lower urinary tract dysfunctions are important to detect, but will be symptomatic and/or obvious on free uroflowmetry with post-void residual measurement, and will subsequently warrant closer evaluation with invasive urodynamics/urethrocystoscopy. It is not necessary to identify asymptomatic DO preoperatively, however. Latent DO may resolve postoperatively. Otherwise, if latent DO becomes symptomatic postoperatively it can be treated medically. Finally, a pressure-flow study and contemporary definitions may actually be misleading in men with PPI and redundant if the free uroflowmetry is normal, indicating normal bladder contractility and outlet. Only if the pathophysiology of PPI is unclear or some form of bladder dysfunction is suspected, urodynamics can add important information in the evaluation of PPI.

Strengths and limitations

We used well-established questionnaires and had high response rates. The attrition analysis showed that the attending patients were representative for our objective to perform urodynamics in patients with severe PPI. Unfortunately, due to some logistical challenges, not all patients underwent complete clinical examination. The small sample undergoing PPI surgery poses a considerable risk of type II statistical errors. Additional significant associations might have escaped us because of the low statistical power.

Paper III

Aim 1

At a median of 26 months after implantation of an AUS, 35% of the patients reported poor generic QOL, similarly to that observed in controls from the general male population. The similarity of the proportions of men with poor versus better generic QOL among cases and controls is encouraging. Admittedly, we do not know how much the implantations have improved generic QOL in the patients. However, because of limited resources, the implantations were restricted to the most bothered patients with incapacitating PPI. We therefore believe that the overwhelming majority of patients had highly reduced generic QOL before surgery. For most of them, the AUS has reduced their PPI problems considerably, thus we believe that it must have affected their normal generic QOL at group level.

Aim 2

In bivariate analyses, urinary and sexual problems were significantly more common in the poor QOL group compared with the better QOL group. The presence of somatic comorbidity, reduced work ability, surgical revision, anxiety and depression were significantly associated with poor generic QOL. Several of these variables are amenable to diagnostic evaluation and eventual counselling or therapy, which should be considered with the aim of improving QOL.

Aim 3

In multivariable analysis, only reduced work ability and increased level of depression remained statistically associated with poor QOL. Our hypothesis of a significant influence of urinary incontinence problems on generic QOL was not supported in the present study.

Do the results of the present study contradict previous reports [175,177,178] of good post-implantation incontinence-related QOL? By no means, but the present study showed clearly that generic QOL, which was our end-point, differs from incontinence-related QOL. Also, in the present study, urinary incontinence was an important factor of generic QOL in bivariate analyses, but was less important when other factors of daily living, such as work ability and mental health, also were taken into account. Furthermore, the present results represent groups of patients, and clinicians have to be aware that urinary incontinence still can be a problem for the individual patient even after AUS implantation.

The present study is the first to report a discrepancy between incontinence-related and generic QOL concerning urinary problems after implantation of AUS for PPI. Although evaluation of incontinence-related QOL is important in uro-oncological practice, the results show that supplement with generic QOL can be of clinical value when the aim is to improve the general well-being of men after RP.

Urologists, oncologists and general practitioners responsible for follow-up of these patients should perhaps take a broader view than only checking for urinary or sexual problems. It is well known that depression can reduce work ability, whereas reduced work ability can also trigger depression, so the primary cause cannot be disentangled in the present cross-sectional study. However, depression is easily tested by self-report or interview, and is amenable to both pharmacological and psychotherapeutic interventions in general practice.

Strength and limitations

We used well-established instruments, and had a high response rate. We also had meaningful control data from the general population concerning generic QOL, and the attrition analysis showed that we could generalize to our total sample. A limitation was the small sample size, with a considerable risk of type II statistical errors. There might be additional significant associations between the independent variables and poor QOL that escaped us because of low statistical power. In contrast, the associations we observed were both statistically and clinically significant despite the low numbers. However, small group sizes resulted in broad 95% confidence intervals in the regression analyses.

The major limitation was a lack of pre-surgery generic QOL ratings, even though we intensively reviewed the medical records. However, it is with little doubt that the men selected for PPI surgery during the study period had incapacitating incontinence, which regularly leads to poor generic QOL.

2.8. Conclusions

Paper I – How should continence and incontinence after radical prostatectomy be evaluated? A prospective study of patient ratings and changes with time

The prevalence of patient reported PPI 12 months after RP was high in this prospective study regardless of the definition applied: 40% of our patients used pads daily and 74% reported any degree of leakage. Severe PPI was reported by 3% to 25%, depending on definition (total incontinence or grading by Ellison et al.). In our opinion incontinence may be reported as any leakage, and not only as pad use, and grading done on a symptom scale. However, our findings cast doubt on the descriptive validity of the PPI stratification introduced by Ellison et al. Particularly their severe PPI stratum seems too broad. Further effort should be made to reach an international consensus on a PPI severity grading. The strongest predictors of persistent PPI were preoperative sexual dysfunction and urinary incontinence but some patients with preoperative incontinence improved after RP. PCa-related and treatment related variables were not associated with PPI in our study.

Paper II - Severe postprostatectomy incontinence: Is there an association between preoperative urodynamic findings and outcome of incontinence surgery?

Urodynamic bladder dysfunction coexisted with intrinsic sphincter deficiency in 67% of the patients with persistent severe PPI, but was not predictive of the outcome of PPI surgery. Our results indicate that invasive urodynamic investigation may not be mandatory before PPI surgery in patients with pure sphincter deficiency and otherwise normal bladder function and outlet assessed by anamnesis, voiding diaries, free uroflowmetry, and post-void residual urine measurement. Urodynamics may thus be omitted in up to two thirds of patients in whom surgery for PPI is considered without compromising the outcome.

However, omitting invasive urodynamic examinations requires careful preoperative counselling of patients regarding the limited risk of detecting a postoperative diagnosis of bladder dysfunction in need of medical therapy. These results should be verified by larger studies.

Paper III - Study of generic quality of life in patients operated on for postprostatectomy incontinence

A total of 35% (95% CI 25–45%) of the cases showed poor QOL compared with 27% (95% CI 24–31%) of the controls in the general population sample. In bivariate analyses we found that urinary and sexual problems were associated with poor generic QOL after surgery for PPI. However, in multivariable analyses these problems did not show significant associations with poor QOL. In contrast, an increased level of depression and reduced current work ability did show significant associations with poor QOL. In case the urologist suspects depression during follow-up of the patient, he should be recommended to contact his regular GP for further evaluation.

2.9. Clinical implications and future research

Paper I – Prevalence of and risk factors for PPI

When studying postprostatectomy incontinence (PPI), with the aim of sober patient counselling, it is important to be clear, concise and not compare apples and pears (i.e. pads and leakage). For both patients and physicians it is important to be aware of widely varying prevalence rates, only depending on definition applied, when comparing published reports.

Rather than making a clear recommendation on how to report and grade PPI, our aim has been to show with concrete numbers the differences in PPI prevalence rates according to the definitions applied. We have primarily tried to document a problem rather than to solve it. In our opinion, major international bodies like the International Continence Society should make more definite recommendations on how to report and grade PPI in the near future. Meanwhile, there should be full candour when reporting PPI, with disclosure of all patients with any leakage, any pad use, and any bother.

Patients with *urinary incontinence* and/or *sexual dysfunction* before RP should be informed about the increased risk of experiencing persistent PPI after RP. Assessment of these risk factors should be part of routine preoperative counselling, similar to counselling given to the PCa patient about treatment modality and expected outcome. When studying risk factors for adverse effects after RP in the future, BMI and baseline testosterone level should also be assessed.

Papers II and III – Urodynamics and outcome of PPI surgery

Urodynamic bladder dysfunction was not predictive of the outcome of PPI surgery; hence invasive urodynamics may be omitted in up to two thirds of patients in whom surgery for PPI is considered without compromising the outcome. However, these results should be verified by studies with larger samples or in randomized controlled trials.

PPI surgery has an acceptable rate of successful outcome, both when regarding satisfaction and pad use. Patients should however be counselled preoperatively that success is defined as use of one pad/day or less and that quite a substantial proportion of patients need pads after PPI surgery. They can also be informed of our study showing generic QOL similar to the general male population. As poor QOL was associated with depression and reduced work ability, these aspects should be considered during follow-up.

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Errata

In the Summary

2.6. Main findings, Paper I, Table 7:

There should not be negative signs before the numbers in the rows after the variables T2b-2c, ≥T3 and RRP.

Reference list:

References 39 and 41 are the same, and references 1 and 15 are the same.

In Paper III, Table 1:

The correct numbers, *n* (%), for the three cancer related variables should be:

Table 1. Characteristics of the total sample and the QoL groups

Variables	Total sample (*n* = 85)	Better QoL (*n* = 55)	Poor QoL (*n* = 30)	p-value
Had pelvic radiotherapy	15 (18)	10 (19)	5 (17)	0.83
Current hormone therapy	10 (12)	5 (9)	5 (19)	0.29
Relapse of prostate cancer	12 (15)	7 (13)	5 (17)	0.75

Appendix: Questionnaires

SPØRSMÅL OM BAKGRUNN OG SYKDOMMER

1. Hvilken sivilstand har du i dag?

Gift eller samboer…… ☐
Skilt eller separert…….. ☐
Enkemann eller partner har gått bort……. ☐
Er i forhold, men bor hver for seg…… ☐
Aldri gift eller samboer…… ☐

2. Hvor mye utdanning har du gjennomført?

Grunnskole, folkeskole eller mindre..…….. ☐
Ungdomsskole, realskole eller tilsvarende….. ☐
Gjennomført videregående eller yrkesskole… ☐
Noe på høgskolenivå…… ☐
Gjennomført høgskole…….. ☐
Gjennomført universitetsutdannelse…..…… ☐

3. Nedenfor finner du en liste med kroniske lidelser og sykdommer.
Vennligst *sett ett kryss for* hver av dem du har eller har hatt i løpet av de siste 12 månedene.

	Har du denne Sykdommen?	Blir du behandlet for denne sykdommen?	Hindrer sykdommen deg i aktiviteter?
	Ja	Ja	Ja
a. Hjerneslag……..	☐	☐	☐
b. Høyt blodtrykk……..	☐	☐	☐
c. Astma, kronisk bronkitt eller KOLS.	☐	☐	☐
d. Sukkersyke……	☐	☐	☐
e. Nyresykdom……..	☐	☐	☐
f. Leversykdom……	☐	☐	☐
g. Anemi eller annen blodsykdom……	☐	☐	☐
h. Sykdom i skjoldbruskkjertelen…….	☐	☐	☐
i. Depresjon……..	☐	☐	☐
j. Slitasjegikt (artrose)……..	☐	☐	☐
k. Ryggsmerter……..	☐	☐	☐
l. Leddbetennelse (revma)……	☐	☐	☐

4. Er du for tiden i inntektsgivende arbeid?

Ja, fulltid…… ☐
Ja, deltid…….. ☐
Nei, men søker jobber…… ☐
Nei, pensjonert……..…….. ☐
Nei, sykmeldt eller på attføring.. ☐
Nei, uføretrygdet…… ☐

SPØRSMÅL OM PROSTATAKREFTEN DIN

5. Har du fått strålebehandling for prostatakreften din? Nei ☐ Ja ☐
6. Har du brukt hormonbehandling for prostatakreften din? Nei ☐ Ja, tidligere ☐ Ja, nå for tiden ☐
7. Har du hatt tilbakefall av prostatakreften din?

Nei ☐ Ja ☐ Hvis Ja, for hvor mange år siden? (skriv tallet) _____

SPØRSMÅL OM URINFUNKSJONEN (Utdrag fra UCLA-PCI)

Dette avsnittet omhandler din urinfunksjon. Det er kun situasjonen de siste 4 ukene du skal ta i betraktning.

1. Hvor ofte har du hatt urinlekkasje i løpet av DE SISTE 4 UKENE?

Hver dag…..... ☐
Omtrent en gang i uken…….. ☐
Sjeldnere enn en gang i uken..... ☐
Aldri……..... ☐

2. Hvordan vil du beskrive din kontroll over blæretømmingen i løpet av DE SISTE 4 UKENE?

Total manglende kontroll (betydelig urinlekkasje) … ☐
Hyppig urinlekkasje……..…….…… ☐
Dråpelekkasje av og til……..…….…..…... ☐
Ingen lekkasje (full kontroll)……..… ☐

3. Hvor mange truseinnlegg, bind eller bleier har du vanligvis brukt *per dag* for lekkasje i løpet av DE SISTE 4 UKENE?

Tre eller flere per dag…….. ☐
En - to per dag……..…….. ……. ☐
Ingen…….. ☐

4. Hvor stort problem har hver av de følgende vært for deg i løpet av DE SISTE 4 UKENE?

Sett ett kryss pr linje	Ikke noe problem	Veldig lite problem	Lite problem	Moderat problem	Stort problem
a. Urinlekkasje med våte benklær……	☐	☐	☐	☐	☐
b. Urinlekkasje som forstyrrer seksuell aktivitet……	☐	☐	☐	☐	☐

5. Hvor stort problem har du totalt sett hatt med urinfunksjonen DE SISTE 4 UKENE?

Ikke noe problem……..…….... ☐
Svært lite problem…….……..… ☐
Lite problem……..……..… ☐
Moderat problem……...…. ☐
Stort problem…….... ☐

SPØRSMÅL OM URINFUNKSJONEN (EPIC-26 Urinary domain)

1. Hvor ofte har du hatt urinlekkasje i løpet av DE SISTE 4 UKENE?

- ☐ Mer enn en gang om dagen……
- ☐ Omtrent en gang om dagen……
- ☐ Mer enn en gang i uken……
- ☐ Omtrent en gang i uken……..
- ☐ Sjelden eller aldri……..

2. Hvordan vil du beskrive din kontroll over vannlatingen i løpet av DE SISTE 4 UKENE?

- ☐ Total manglende kontroll (betydelig urinlekkasje) …
- ☐ Hyppig urinlekkasje……..……..……
- ☐ Dråpelekkasje av og til……..……..……..…...
- ☐ Ingen lekkasje (full kontroll)……..…

3. Hvor mange truseinnlegg, bind eller bleier har du vanligvis brukt *per dag* for lekkasje i løpet av DE SISTE 4 UKENE?

- ☐ Ingen……..
- ☐ En per dag……..…….. ……
- ☐ To per dag…….....
- ☐ Tre eller flere per dag…….

4. Hvor stort problem har hver av de følgende vært for deg i løpet av DE SISTE 4 UKENE?

Sett ett kryss pr linje	Ikke noe problem	Veldig lite problem	Lite problem	Moderat problem	Stort problem
a. Drypping eller urinlekkasje……	☐	☐	☐	☐	☐
b. Smerte eller brennende følelse ved vannlating……	☐	☐	☐	☐	☐
c. Blod i urinen……..	☐	☐	☐	☐	☐
d. Svak urinstråle eller vansker med å tømme blæra?.....	☐	☐	☐	☐	☐
e. Må du late vannet ofte i løpet av dagen?.....	☐	☐	☐	☐	☐

5. Samlet sett hvor stort problem har du hatt med urinfunksjonen DE SISTE 4 UKENE?

- ☐ Ikke noe problem……..……...
- ☐ Svært lite problem……..…
- ☐ Lite problem……..……..…
- ☐ Moderat problem……...…
- ☐ Stort problem……...

SPØRSMÅL OM SEKSUALFUNKSJONEN (Utdrag fra UCLA-PCI)

Det neste avsnittet om seksualfunksjon inneholder mange spørsmål av personlig karakter. Vi minner om at svarene på dette spørreskjemaet vil bli behandlet konfidensielt og vil bare bli brukt til forskningsformål: Vær snill å svare så ærlig som du kan om de siste 4 ukene.

1. Hvordan vil du gradere det følgende i løpet av de siste 4 ukene?

Sett ett kryss på hver linje	Svært dårlig	Dårlig	Rimelig	God	Svært god
a. Grad av seksuell interesse (lyst)…..	☐	☐	☐	☐	☐
b. Din evne til å få ereksjon (reisning)…..	☐	☐	☐	☐	☐
c. Din evne til å få orgasme (klimaks)…..	☐	☐	☐	☐	☐

2. Hvordan er vanligvis GRADEN av stivhet ved ereksjon?

Ingen ereksjon (reisning)…… ☐
Ikke stiv nok til noen seksuell aktivitet….. ☐
Bare stiv nok til onanering og forspill…… ☐
Tilstrekkelig stivhet for samleie……. ☐

3. Hvor OFTE har du oppnådd ereksjon når det har vært ønskelig?

Aldri ereksjon når jeg har ønsket det…… ☐
Mindre enn halvparten av tiden …… ☐
Omtrent halvparten av tiden ……. ☐
Mer enn halvparten av tiden ……. ☐
Alltid ereksjon når det har vært ønskelig …. ☐

4. Hvor ofte har du våknet om morgenen eller natten med ereksjon?

Aldri……..…….…..... ☐
Sjelden (mindre enn 25% av tiden)..... ☐
Ikke ofte (mindre enn halvparten av tiden)…. ☐
Ofte (mer enn halvparten av tiden)…..... ☐
Veldig ofte (mer enn 75% av tiden)……..… ☐

5. Har du gjennomført samleie i løpet av de siste 4 ukene?

Nei.....…….…..…..... ☐
Ja, en gang……..…..…. ☐
Ja, mer enn en gang…..……..…..…. ☐

6. Hvordan vil du karakterisere din evne til å fungere seksuelt de siste 4 ukene?

Svært dårlig……..…..…..... ☐
Dårlig……..…. …. ☐
Rimelig……..……..… …. ☐
God…….……...…. …. ☐
Svært god……..…….. … ☐

7. Har du brukt tabletter utskrevet av lege for å bedre seksuell funksjon (potens)?

Alltid …… ☐
Oftest …… ☐
Sjelden …… ☐
Aldri …… ☐

8. Har du satt sprøyte/injeksjon i penis for å få bedre ereksjon?

Alltid …… ☐
Oftest …… ☐
Sjelden …… ☐
Aldri …… ☐

9. Hvordan vil du beskrive din evne til å gjennomføre samleie uten, eller eventuelt med tabletter eller sprøyter i løpet av de siste 4 ukene?

a) Uten tabletter eller sprøyter
- Ikke aktuelt …… ☐
- Ikke ereksjon, samleie ikke mulig…… ☐
- Samleie mulig i mindre enn halvparten av forsøkene.. ☐
- Samleie mulig ved de fleste forsøk …… ☐
- Samleie alltid mulig …… ☐

b) Med tabletter for potens (ikke sprøyter)
- Ikke aktuelt …… ☐
- Ikke ereksjon, samleie ikke mulig…… ☐
- Samleie mulig i mindre enn halvparten av forsøkene.. ☐
- Samleie mulig ved de fleste forsøk …… ☐
- Samleie alltid mulig …… ☐

c) Etter bruk av sprøyter i penis
- Ikke aktuelt …… ☐
- Ikke ereksjon, samleie ikke mulig…… ☐
- Samleie mulig i mindre enn halvparten av forsøkene.. ☐
- Samleie mulig ved de fleste forsøk …… ☐
- Samleie alltid mulig …… ☐

20. Hvor stort problem har din seksualfunksjon vært for deg de siste 4 ukene?

Ikke noe problem…… ☐
Svært lite problem..…….. ☐
Lite problem……. ☐
Moderat problem…..…… ☐
Stort problem…… ☐

20. Har du hatt smerter eller ubehag i forbindelse med orgasme/ utløsning?

Alltid……..…… ☐
Oftest (mer enn halvparten av gangene)…….. ☐
Ganske ofte (omtrent halvparten av gangene)……. ☐
Sjelden (mindre enn halvparten av gangene)…… ☐
Aldri…… ☐

SPØRSMÅL OM SEKSUALFUNKSJONEN (EPIC-26 Sexual domain)

Denne delen handler om din nåværende seksualfunksjon og din seksuelle tilfredsstillelse. Mange av spørsmålene er svært personlige, men vi minner om at svarene dine blir behandlet konfidensielt og bare blir brukt til forskning.

15. Dersom du bruker hjelpemidler for ereksjonen, merk av hvilke du har brukt i løpet av DE SISTE 4 UKENE?

Tabletter	Ja	☐	Nei	☐
Injeksjoner/ Sprøyter	Ja	☐	Nei	☐
Vakumpumpe	Ja	☐	Nei	☐
Bondil urethralstift	Ja	☐	Nei	☐

16. Hvordan vil du gradere det følgende i løpet av DE SISTE 4 UKENE?

Sett ett kryss på hver linje	Svært dårlig	Dårlig	Rimelig	God	Svært god
a. Din evne til å få ereksjon (reisning)…..	☐	☐	☐	☐	☐
b. Din evne til å få orgasme (klimaks)…..	☐	☐	☐	☐	☐

17. Hvordan har KVALITETEN på ereksjonen vært i løpet av DE SISTE 4 UKENE?

Ingen ereksjon (reisning)……	☐
Ikke stiv nok til noen seksuell aktivitet…..	☐
Bare stiv nok til onanering og forspill……	☐
Tilstrekkelig stivhet for samleie…….	☐

18. Hvor OFTE har du oppnådd ereksjon når det har vært ønskelig?

Aldri ereksjon når jeg har ønsket det……	☐
Mindre enn halvparten av tiden ……	☐
Omtrent halvparten av tiden …….	☐
Mer enn halvparten av tiden …….	☐
Alltid ereksjon når jeg har ønsket det ……..	☐

19. Samlet sett hvordan vil du karakterisere din evne til å fungere seksuelt DE SISTE 4 UKENE?

Svært dårlig……..……....	☐
Dårlig……..… ….	☐
Rimelig……..……..… ….	☐
God…….……...…. ….	☐
Svært god……..…….. …	☐

20. Samlet sett hvor stort problem har din seksualfunksjon eller mangel på seksualfunksjon vært for deg DE SISTE 4 UKENE?

Ikke noe problem…….……..…	☐
Svært lite problem..……..	☐
Lite problem…….	☐
Moderat problem…..……	☐
Stort problem……	☐

SPØRSMÅL OM TARMFUNKSJONEN (EPIC-26 Bowel domain)

13. Hvor stort problem, om noe, har hver av de følgende vært for deg i løpet av DE SISTE 4 UKENE?

Sett ett kryss på hver linje	Ikke noe problem	Veldig lite problem	Lite problem	Moderat problem	Stort problem
a. Sterk, umiddelbar avføringstrang…..	☐	☐	☐	☐	☐
b. Hyppigere avføring……	☐	☐	☐	☐	☐
c. Mistet kontroll over avføringen…….	☐	☐	☐	☐	☐
d. Blod i avføringen……	☐	☐	☐	☐	☐
e. Smerter i magen, bekkenet eller i endetarmen……..	☐	☐	☐	☐	☐

14. Samlet sett, hvor stort problem har avføringsfunksjonen vært for deg i løpet av DE SISTE 4 UKENE?

Ikke noe problem…… ☐
Svært lite problem……. ☐
Lite problem……..……. ☐
Moderat problem…… ☐
Stort problem…….. ☐

SPØRSMÅL OM ANDRE FUNKSJONER (EPIC-26 Hormonal domain)

26. Hvor stort problem, om noe, har hvert av de følgende vært for deg DE SISTE 4 UKENE?

Sett ett kryss på hver linje	Ikke noe problem	Veldig lite problem	Lite problem	Moderat problem	Stort problem
a. Hetetokter……..	☐	☐	☐	☐	☐
b. Ømme/svulne bryster……	☐	☐	☐	☐	☐
c. Følt deg nedstemt……..	☐	☐	☐	☐	☐
d. Manglet energi……..	☐	☐	☐	☐	☐
e. Vektforandring……..	☐	☐	☐	☐	☐

SPØRSMÅL OM HELSEN (SF-12)

De første spørsmålene er om helsen din generelt, BÅDE RELATERT og IKKE RELATERT til din prostatakreft. Vi er klar over at andre sykdommer som du kan ha i tillegg til din prostatakreft, kan påvirke svarene dine. Hvert spørsmål skal besvares ved å sette ett kryss ved det som passer best for deg. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

28. Stort sett, vil du si at din helse de siste 4 ukene er?

Utmerket…… ☐
Meget god …….. ☐
God…….…… ☐
Nokså god…….. ☐
Dårlig…… ☐

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

2. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid
Ja, begrenser meg mye……. ☐
Ja, begrenser meg lit……. ☐
Nei, begrenser meg ikke i det hele tatt. ☐

3. Gå opp trappen flere etasjer
Ja, begrenser meg mye……. ☐
Ja, begrenser meg litt …….. ☐
Nei, begrenser meg ikke i det hele tatt. ☐

4. Har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse i løpet av DE SISTE 4 UKENE?

	Ja	Nei
a. Du har utrettet mindre enn du hadde ønsket…… ……	☐	☐
b. Du har vært hindret i visse typer arbeid eller andre gjøremål ….	☐	☐

5. I løpet av DE SISTE 4 UKENE har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (f.eks. fordi du har følt deg deprimert eller engstelig)? Sett ett kryss på hver linje

	Ja	Nei
a. Du har utrettet mindre enn du hadde ønsket……	☐	☐
b. Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig……	☐	☐

6. I løpet av DE SISTE 4 UKENE, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt……... ☐
Litt…….. ☐
Endel……..…….. ☐
Mye……..…….. ☐
Svært mye..…… ☐

7. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det DE SISTE 4 UKENE. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.

Hvor ofte i løpet av DE SISTE 4 UKENE? Sett ett kryss på hver linje

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Har du følt deg rolig og harmonisk?.	☐	☐	☐	☐	☐	☐
b. Har du følt deg full av tiltakslyst?	☐	☐	☐	☐	☐	☐
c. Har du følt deg nedfor og trist?	☐	☐	☐	☐	☐	☐

8. I løpet av DE SISTE 4 UKENE, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

Hele tiden…….. ☐
Nesten hele tiden…… ☐
En del av tiden…….. ☐
Litt av tiden…….. ☐
Ikke i det hele tatt..…… ☐

SPØRSMÅL OM VÆREMÅTER (EPQ-N)

Spørsmålene nedenfor dreier seg om hvordan du vanligvis opptrer, føler og handler. Vennligst kryss av for enten **Ja** eller **Nei** for hvert spørsmål. Svar hurtig og ikke tenk for lenge over den nøyaktige meningen med hvert spørsmål.

27. Sett ett kryss på hver linje	**Ja**	**Nei**
a. Blir dine følelser lett såret?.....	☐	☐
b. Hender det ofte at du ”går trøtt”?.....	☐	☐
c. Er du ofte bekymret?.....	☐	☐
d. Bekymrer du deg for at fryktelige ting kan skje?.....	☐	☐
e. Har du ofte følt deg trøtt og giddesløs uten grunn?.....	☐	☐
f. Bekymrer du deg lenge etter en pinlig opplevelse?.....	☐	☐

SPØRSMÅL OM HVORDAN DU FØLER DEG (HADS)

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser **den siste uka**. Ikke tenk for lenge på svaret - de spontane svarene er best. Sett ett kryss for hvert spørsmål.

36. Jeg føler meg nervøs og urolig
- ☐ Mesteparten av tiden
- ☐ Mye av tiden
- ☐ Fra tid til annen
- ☐ Ikke i det hele tatt

37. Jeg gleder meg fortsatt over tingene slik jeg pleide før
- ☐ Avgjort like mye
- ☐ Ikke fullt så mye
- ☐ Bare lite grann
- ☐ Ikke i det hele tatt

38. Jeg har en urofølelse som om noe forferdelig vil skje
- ☐ Ja, og noe svært ille
- ☐ Ja, ikke så veldig ille
- ☐ Litt, bekymrer meg lite
- ☐ Ikke i det hele tatt

39. Jeg kan le og se det morsomme i situasjoner
- ☐ Like mye nå som før
- ☐ Ikke like mye nå som før
- ☐ Avgjort ikke som før
- ☐ Ikke i det hele tatt

40. Jeg har hodet fullt av bekymringer
- ☐ Veldig ofte
- ☐ Ganske ofte
- ☐ Av og til
- ☐ En gang i blant

41. Jeg er i godt humør
- ☐ Aldri
- ☐ Noen ganger
- ☐ Ganske ofte
- ☐ For det meste

42. Jeg kan sitte i fred og ro og kjenne meg avslappet
- ☐ Ja, helt klart
- ☐ Vanligvis
- ☐ Ikke så ofte
- ☐ Ikke i det hele tatt

43. Jeg føler meg som om alt går langsommere
- ☐ Nesten hele tiden
- ☐ Svært ofte
- ☐ Fra tid til annen
- ☐ Ikke i det hele tatt

44. Jeg føler meg urolig som om jeg har sommerfugler i magen
- ☐ Ikke i det hele tatt
- ☐ Fra tid til annen
- ☐ Ganske ofte
- ☐ Svært ofte

45. Jeg bryr meg ikke lenger om hvordan jeg ser ut
- ☐ Ja, har sluttet å bry meg
- ☐ Ikke som jeg burde
- ☐ Kan hende ikke nok
- ☐ Bryr meg som før

46. Jeg er rastløs som om jeg stadig må være aktiv
- ☐ Uten tvil svært mye
- ☐ Ganske mye
- ☐ Ikke så veldig mye
- ☐ Ikke i det hele tatt

47. Jeg ser med glede frem til hendelser og ting
- ☐ Like mye som før
- ☐ Heller mindre enn før
- ☐ Avgjort mindre enn før
- ☐ Nesten ikke i det hele tatt

48. Jeg kan plutselig få en følelsen av panikk
- ☐ Uten tvil svært ofte
- ☐ Ganske ofte
- ☐ Ikke så veldig ofte
- ☐ Ikke i det hele tatt

49. Jeg kan glede meg over gode bøker, radio og TV
- ☐ Ofte
- ☐ Fra tid til annen
- ☐ Ikke så ofte
- ☐ Svært sjelden

SPØRSMÅL OM ARBEIDSEVNE (WAI)

50. Hvordan vurderer du din arbeidsevne med tanke på de fysiske krav ved ditt arbeid?

- ☐ Meget god
- ☐ Ganske god
- ☐ Rimelig god
- ☐ Nokså dårlig
- ☐ Svært dårlig
- ☐ Ikke i arbeid

51. Hvordan vurderer du din arbeidsevne med tanke på de psykiske krav ved ditt arbeid?

- ☐ Meget god
- ☐ Ganske god
- ☐ Rimelig god
- ☐ Nokså dårlig
- ☐ Svært dårlig
- ☐ Ikke i arbeid

52. La oss gå ut fra at arbeidsevnen din på ditt beste ville fått 10 poeng. Hvor mange poeng vil du da gi din nåværende arbeidsevne? (0 innebærer at du ikke er i stand til å arbeide i det hele tatt. Sett ett kryss under det tallet som best tilsvarer din nåværende arbeidsevne. Besvar spørsmålet også om du ikke lenger er i arbeid.)

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

SPØRSMÅL OM TILFREDSHET

53. Samlet sett, hvor tilfreds er du med informasjonen om og behandlingen av din prostatakreft som du har fått av de ansatte i helsevesenet (leger, sykepleiere, uroterapeuter, stråleterapeuter)

Ekstremt utilfreds	Utilfreds	Usikker	Tilfreds	Meget tilfreds
☐	☐	☐	☐	☐

54. Samlet sett, hvor tilfreds er du med informasjonen om og behandlingen av din urinlekkasje som du har fått av de ansatte i helsevesenet (leger, sykepleiere, uroterapeuter)

Ekstremt utilfreds	Utilfreds	Usikker	Tilfreds	Meget tilfreds
☐	☐	☐	☐	☐

SPØRSMÅL OM OPERASJONEN FOR URINLEKKASJE

Spørsmålene markert med (a) AMS800) ble bare sendt til pasienter med sfinkterprotese og spørsmålene markert med (b) AdVance) ble bare sendt til pasientene med slynge.For øvrig var spørsmålene like for alle pasientene.

1. Er du fornøyd med operasjonen for urinlekkasje?

Veldig fornøyd ☐ Litt fornøyd ☐ Usikker ☐ Misfornøyd ☐

2. (a) AMS800) Synes du lukkeprotesen er enkel å bruke?

Ja ☐ Nei ☐

2. (b) AdVance) Har du hatt problemer med å tømme blæren de siste 4 ukene?

Ja ☐ Nei ☐

3. (a) AMS800) Har du noe ubehag i forbindelse med bruk av protesen/pumpen?

Ja ☐ Nei ☐

3. (b) AdVance) Har du hatt smerter pga. operasjonen de siste 4 ukene?

Ja ☐ Nei ☐

4. Vil du anbefale andre med urinlekkasje en slik operasjon?

Ja ☐ Ja, med forbehold ☐ Usikker ☐ Nei ☐

5. Ville du valgt en slik operasjon på nytt i ettertid?

Ja ☐ Nei ☐

6. Har inngrepet hatt noen innvirkning på seksualfunksjonen din?

Ja, den er blitt bedre ☐ Nei, ingen innvirkning ☐ Ja, den er blitt dårligere ☐